Paid Circulation, 25,587

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 245 • DECEMBER 20, 1951 • NUMBER 25

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Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

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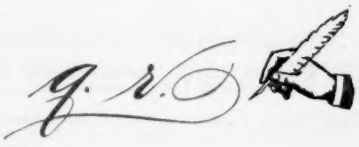

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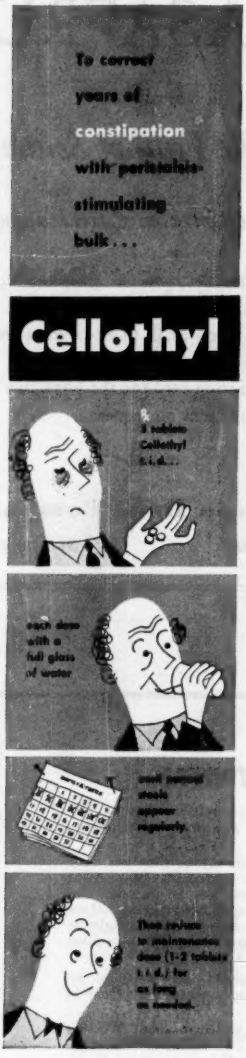
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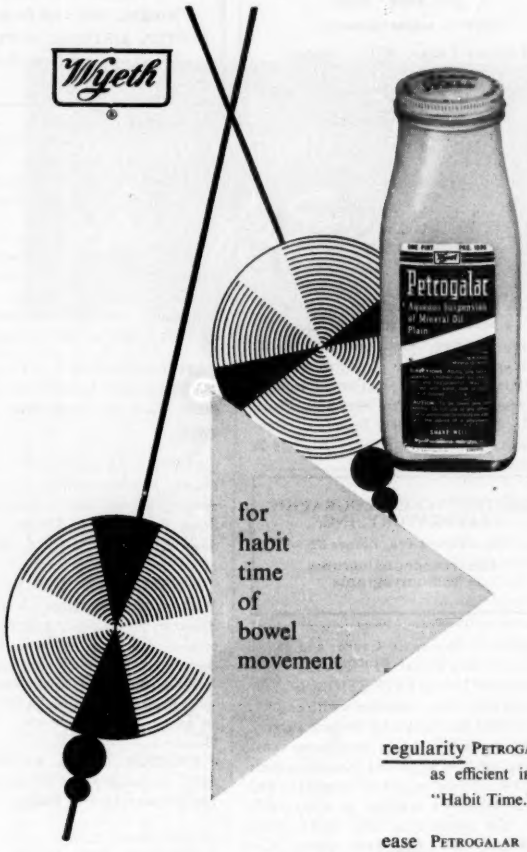

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The New England
Journal of Medicine

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Volume 245 DECEMBER 20, 1951 Number 25

SUBGLOTTIC MEMBRANE*

A Complication of Endotracheal Intubation

BENJAMIN ETSTEN, M.D.,† AND DONALD MAHLER (MC), U.S.A.‡

BOSTON

ENDOTRACHEAL intubation is a technic commonly used during inhalation anesthesia for the maintenance of a patent airway, management of respiratory exchange and aspiration of tracheobronchial secretions. In addition, this method is frequently used for aspiration of secretions in patients with atelectasis, pulmonary edema or excess secretions associated with other pulmonary conditions. It is also a valuable measure for maintaining a patent airway in the comatose patient.

Acute laryngeal complications following the skillful use of this method have been rare. Edema of the glottis is mentioned as a possible complication.[1] Shaw[2] reported a case of massive laryngeal edema that immediately followed traumatic intubation and prolonged anesthesia. Pharyngitis and laryngitis are more frequent minor complications. Postoperative laryngoscopy of 100 patients[3] revealed such complications as congestion of the glottis, submucosal puncture wounds, crushed epiglottis and soft-tissue contusions outside the larynx. It is obvious that such sequelae are the results of traumatic technic.

Another type of postendotracheal complication presented in this report is the formation of a subglottic membrane.

In a series of 800 endotracheal intubations in adults, 3 patients developed acute obstruction of the upper respiratory tract from twenty-four to forty-eight hours after endotracheal anesthesia. The clinical picture was that of laryngeal edema: cough, hoarseness, stridor, dyspnea and suprasternal retraction. Without immediate therapy the complications of acute anoxia would have ensued. On direct laryngoscopic examination, the glottic chink, epiglottis and larynx appeared normal and there was no evidence of laryngeal edema. Bronchoscopy, however, revealed an adherent subglottic membrane as the cause of the obstruction.

Obstructed breathing requires immediate diagnosis and treatment. The administration of oxygen and hypnotics to overcome the restlessness, anxiety, dyspnea and tachycardia are palliative for a short time only; acute anoxia will ultimately result in spite of these measures, and an emergency tracheotomy will be required as a life-saving procedure. An adherent subglottic membrane occurring as a postendotracheal complication can easily be missed, particularly if tracheotomy is performed.

Because prompt recognition of subglottic-membrane formation is imperative for the immediate treatment of obstructed breathing after endotracheal intubation, descriptions of the clinical course, probable etiologic factors and treatment in 3 cases are presented.

CASE REPORTS

CASE 1. A. C., a 51-year-old woman, was admitted to the New England Center Hospital on January 31, 1950. A diagnosis of cholecystitis, biliary calculus and anemia, Mediterranean type, was made. At the age of 41 the patient had a hysterectomy and the postoperative course was uneventful. The systemic review was essentially negative. On admission the temperature was 99°F., the pulse 75 and the respirations 18. Physical examination revealed a heart enlarged 1 cm. outside the midclavicular line on the left and an obese abdomen; the liver edge was palpable 2 fingerbreadths below the costal margin. The urine had a trace of albumin. The hemoglobin was 9.9 gm. An oral cholecystogram showed a nonfilling gall bladder with areas of radiolucency.

On February 3, 1950, a cholecystectomy was performed. Anesthesia was induced with pentothal sodium and d-tubocurarine chloride. A Magill endotracheal tube fitted with an elongated low-pressure inflatable balloon, lubricated with Nupercainal ointment, was introduced into the trachea. An airtight fit between the trachea and endotracheal tube was obtained without inflating the cuff. The operating time was 3 hours; the course during surgery and anesthesia was uneventful. At the conclusion of the procedure, when the endotracheal tube was withdrawn from the trachea and larynx, unusual resistance was felt.

On the operative day the patient's temperature was 98.6°F., the pulse rate was 70 to 80 per minute and the respirations were 24 per minute. There was considerable watery tracheobronchial secretion, which the patient expectorated with ease. Twenty-four hours after operation the pulse rate suddenly rose to 120, the blood pressure increased to 180/98 and the respirations accelerated to 38. Signs of upper-respiratory-tract obstruction developed, with hoarseness, stridor, dyspnea and suprasternal retraction. Bronchoscopy was performed. A fibrinous exudate below the true cords adherent to the anterior wall of the cricothyroid membrane was visualized. Removal of this membrane resulted in an immediate

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clinical improvement; the respirations fell to 24 and the pulse to 70. Respiratory obstructive symptoms recurred 24 hours later, associated with an increase in pulse and respirations. Bronchoscopy was repeated, revealing another fibrinous exudate at the same area on the cricothyroid membrane. This was removed in one piece. After this procedure, the patient had no further respiratory difficulties. She was ambulatory on the 5th postoperative day and discharged on the 11th.

CASE 2. S. T., a 59-year-old woman, was admitted on March 5, 1950, to the New England Center Hospital. The diagnosis was postoperative stricture of choledochoduodenostomy and

FIGURE 1. *Subglottic Membrane (x50).*

choledocholithiasis. The systemic review was noncontributory. Physical examination of the nose, throat, lungs and heart revealed normal findings. The temperature was 98.6°F., the pulse rate 80 and the respirations 20.

On March 8, a revision of the choledochoduodenostomy was performed. Anesthesia was induced with d-tubocurarine chloride, pentothal sodium, nitrous oxide and oxygen. A Magill endotracheal tube, fitted with an elongated low-pressure inflatable cuff and lubricated with Nupercainal ointment, was easily introduced into the trachea. It was not necessary to inflate the cuff in order to maintain an airtight fit between the trachea and the anesthetic to-and-fro absorption apparatus. The 5-hour anesthesia was uneventful. At the conclusion of the procedure, resistance was encountered during the withdrawal of the endotracheal tube. The immediate postoperative course was uneventful. Eighteen hours after the operation the patient complained of slight hoarseness. Twenty-four hours postoperatively the patient had slight stridor and suprasternal retraction during inspiration. The temperature rose to 101.6°; the pulse increased to 100 and the respirations to 40. Bronchoscopy under topical 5 per cent cocaine anesthesia was performed. A subglottic fibrinous membrane was removed from the anterolateral aspect of the cricothyroid mucosa. The patient had respiratory relief immediately after the procedure. Her pulse fell to 80 and her respirations rate to 24. On the third postoperative day the patient again developed symptoms of upper-respiratory-tract obstruction. Direct laryngoscopy was carried out. Adherent débris, which was visualized at the posterior commissure, was removed by suction, and the voice became normal. The clinical course was uneventful and the patient was discharged on the 14th postoperative day.

CASE 3. F. D., a 67-year-old woman, was admitted to the New England Center Hospital on February 20, 1950. The diagnosis of hiatus hernia was made. The chief complaint was increasing dyspnea on exertion. Physical examination revealed an enlarged liver extending 2 fingerbreadths below the costal margin and a Grade II apical systolic murmur. Gastrointestinal x-ray films revealed a diverticulum of the esophagus with a large hiatus hernia. The chest x-ray films showed clear lung fields. The temperature was 98°F., the pulse 72 and the respirations 20; the blood pressure was 148/78 on the preoperative day.

On March 24, a transthoracic repair of the hiatus hernia and splenectomy were performed. The anesthesia used was pentothal sodium, d-tubocurarine chloride, nitrous oxide and oxygen. A Magill endotracheal tube fitted with an elongated low-pressure inflatable cuff was easily introduced into the trachea. The cuff was not inflated. The operative and anesthesia course were uneventful. The patient was returned to her room in excellent condition. On March 25, 24 hours postoperatively, the patient complained of slight hoarseness. At this time the pulse rate was from 72 to 90 and the respirations were from 20 to 24; the temperature was 99°F. On March 27, 60 hours postoperatively, the patient developed stridor, dyspnea and suprasternal retraction. The pulse rose

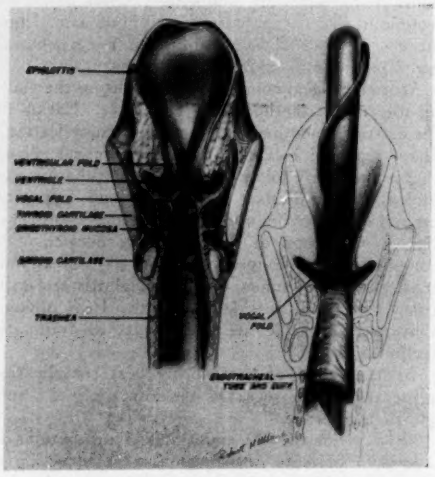

FIGURE 2. *Coronal Section of Adult Larynx. The left view shows the anatomic hourglass configuration of the supraglottic and infraglottic areas.*

to 100 and the respirations to 30 per minute. A bronchoscopy showed no evidence of laryngeal edema, but an accumulation of débris with membrane formation was found in the subglottic region. After removal of this membrane the breathing became normal; the pulse rate fell to 80 and the respirations to 20. On the 4th postoperative day respiratory obstruction recurred, and another membrane was incompletely removed during bronchoscopy. On the 5th postoperative day a tracheotomy was performed, but another bronchoscopy with complete removal of the membrane might have been adequate.

DISCUSSION

These 3 cases of acute obstructed breathing following endotracheal anesthesia present a number of

common factors: the onset of respiratory distress, as evidenced by hoarseness and tachypnea occurring twenty-four to forty-eight hours after the endotracheal extubation; Magill rubber endotracheal tubes fitted with elongated low-pressure inflatable cuffs were used; the endotracheal tubes and cuffs fitted so snugly in the trachea that it was not necessary to inflate the cuff; a sense of firm resistance was encountered during extubation; metal stylets with blunted ends were used as endotracheal introducers to conform with the anterior curve of the pharynx and larynx; all 3 patients were obese, short-necked women and had indwelling Levine tubes during and after the operation procedure; and microscopical examination of the subglottic membrane revealed a fibropurulent exudate such as is seen in streptococcal infections of the bronchi (Fig. 1).

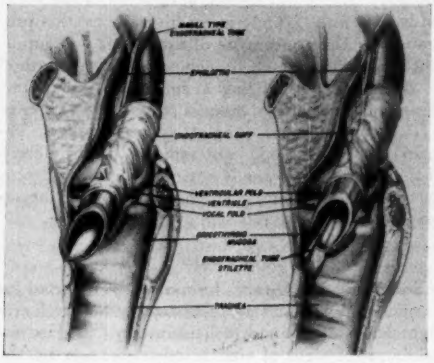

FIGURE 3. *Sagittal Section of Adult Larynx. Position of tip of endotracheal tube or stylet during intubation.*

To explain the formation of a subglottic membrane it is necessary to review briefly the anatomy of the larynx. The subglottic area is the narrowest point of the larynx (Fig. 2). It is completely surrounded by the cricoid cartilage, which forms a rigid circle with the mucosa loosely attached. The subglottic area is particularly vulnerable to injury, which causes infection and results in membrane formation or edema. A slight narrowing of the lumen at this point is likely to obstruct respiration.[4] This area can easily be injured during the process of intubation, by either the tip of the curved endotracheal tube or the projecting point of the stylet (Fig. 3). Trauma to the subglottic mucosa can follow an apparently nontraumatic intubation. Prolonged pressure against the subglottic mucosa by a deflated and wrinkled endotracheal cuff can produce minute superficial abrasions (Fig. 2). This is more likely to occur when the endotracheal tube and cuff are of too large a caliber for the diameter of the trachea. This etiologic factor can be avoided by the use of a small, smooth cuff and an endotracheal tube properly sized, according to the individual patient, and by positioning of the entire cuff below the cricothyroid mucosa (Fig. 4).

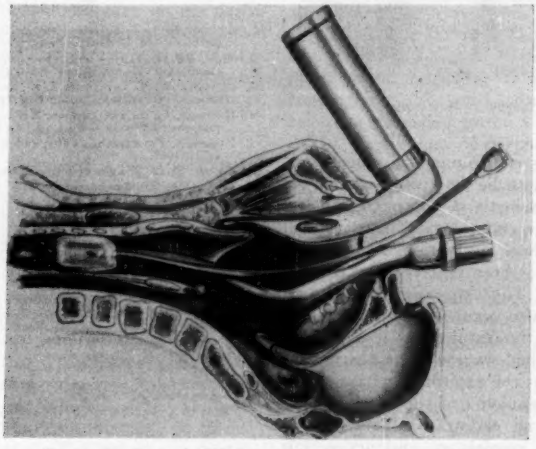

FIGURE 4. *Anatomic Relations of MacIntosh Laryngoscope and Magill-Type Endotracheal Tube with Inflatable Cuff.*

After the initial injury to the infraglottic mucosa by any one of the mechanisms described, leukocytes and desquamated epithelial cells accumulate about the abraded area. A subglottic membrane most probably develops in this manner. The mem-

brane is more likely to form on the anterior aspect of the cricothyroid area, as during introduction of the endotracheal tube its tip will first impinge on the anterior portion of the infraglottic region. The medial aspect of the membrane, when free, comes in contact with the inferior surface of the vocal cords (Fig. 5). Respiration is impeded in part by the membrane and in part by the reflex adduction of the vocal cords. This phenomenon becomes clinically evident with the onset of hoarseness, tachypnea and stridor from twenty-four to forty-eight hours after extubation.

In contrast to subglottic-membrane formation, laryngeal edema usually occurs within a few hours after a traumatic intubation. The clinical picture

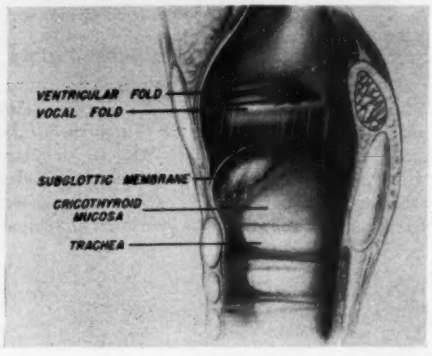

FIGURE 5. *Subglottic Membrane.*

of edema of the glottis is also one of dyspnea, stridor, tachypnea, tachycardia and suprasternal retraction. Necrotic tracheitis is another complication that may produce respiratory distress several hours after endotracheal intubation.[5] Slough of the tracheal mucosa has been reported as a complication of intubation.[6] The respiratory obstruction produced by it may also occur within twenty-four to forty-eight hours after extubation; it is characterized by a high-pitched wheeze. The obstructive signs appear mainly in the expiratory phase of the respiratory cycle. Granuloma of the vocal cords is a late complication of endotracheal technics.[7-17] It does not produce respiratory obstruction but causes progressive hoarseness. A foreign body within the area of the glottic chink may produce signs similar to those of laryngeal edema or subglottic membrane.

The differential diagnosis of the complications mentioned can be greatly aided by direct laryngoscopy. Laryngeal edema, granuloma of the vocal cords or a foreign body is readily seen by this procedure. If the appearance of the glottis and supraglottic area is normal, bronchoscopy is the method of choice for visualizing a subglottic membrane, slough of the bronchial mucosa or necrotic tracheitis.

The treatment of subglottic membrane is immediate bronchoscopy and removal of the débris. If the entire membrane is not removed it may recur in twenty-four hours. Tracheotomy is not necessary after complete removal of the membrane.

SUMMARY

Subglottic membrane formation is reported as a complication that may occur twenty-four to forty-eight hours after endotracheal intubation. Hoarseness and the signs of obstructed respiration are the diagnostic features. A subglottic membrane may erroneously be diagnosed as edema of the glottis. This is more likely to occur if a tracheotomy is performed without previous visualization of the larynx. Direct laryngoscopy and suction bronchoscopy are the methods of choice for diagnosis and treatment.

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THE EFFECTS OF PYROMEN ADMINISTERED INTRAVENOUSLY IN SUBPYREXIAL DOSES TO DEPRESSED PATIENTS*

A Preliminary Study

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PYROMEN is a sterile, nonprotein, nonanaphylactogenic extract of *Pseudomonas aeruginosa* and *Proteus vulgaris* prepared as a colloidal dispersion in normal saline for intravenous use.[1, 2] Pharmacologically, it is a pyrogen of a high degree of reliability and a low order of toxicity. Chemical analysis has identified it as a complex polysaccharide.[3-4] Study of the histologic and physiologic effects in animals revealed some ACTH-like effects.[5-6] Clinical evaluation was directed toward its efficacy not only as a pyrexial agent but also as a stimulant of the pituitary–adrenal axis in those diseases believed to respond to ACTH.[7-11] In certain allergic states it proved beneficial in subpyrogenic doses.[12]

A sense of well-being following shortly after Pyromen-induced fever was reported by several investigators. Whether or not the effect might be obtained without fever was not known, nor were data available to determine either the consistency or duration of the reaction.[13-15]

The present study was undertaken on the postulate that if Pyromen in subpyrogenic doses would elicit the euphoric effect it might serve as an adjunct in the treatment of some depressions and possibly provide some information about their pathogenesis.

METHOD

This evaluation of Pyromen§ is of a preliminary nature. As a result, laboratory studies including psychometric tests were not made in detail. The fact that dosage schedules in the subpyrexial range had not been well established necessitated some experimentation to determine both the optimum amount and the frequency of dosage. On the assumption that the same amount would be effective for patients with allergic manifestations and those with depression (if the latter responded to the agent at all), 15 patients with objectively evident allergic symptoms were included in the study as "controls." All patients were students or faculty members of the university. This automatically provided age limitations, but it afforded reasonable assurance that the subjects would remain under observation for certain pre-established periods of time. With few exceptions each subject had received a thorough physical examination in our clinic within the preceding year. The depressed subjects who were selected for a trial of Pyromen had been under psychiatric care for a period ranging from weeks to years. Several had received nicotinic acid or dexedrine or both, without relief.

Sixty-two patients were treated with Pyromen between December 1, 1949, and June 30, 1950. Sixteen were eliminated because the observation periods were too limited to permit evaluation. Of the 46 subjects included, 29 were men and 17 were women. The youngest was seventeen and the oldest fifty-five years of age. Thirty-four were under thirty-five years of age.

Thirty-one presented the chief complaint of depression of sufficient severity to inhibit the pursuit of academic activity. These fell into 2 categories: 21 who considered depression their major symptom and 10 who had other conditions to which they considered it secondary. Six of the former group were known to have been suicidal; one attempted to slash her wrists on the day on which treatment was instituted. The chief complaints of the second group were: hirsutism 1, fatigue 3, inability to concentrate 1, anxiety 1, chronic "colds" 1, restlessness 1, compulsive eating 1 and dermatitis 1.

The distribution of psychiatric diagnoses of the depressed patients was as follows: anxiety tension state 17; hysteria 1; manic-depressive reaction 4; compulsive-obsessive neurosis 3; benign depression 1; psychopathic personality 1; schizophrenia 4.

The chief complaints of the 15 who were not depressed were: muscle pain 1, chronic nasal congestion with periodic exacerbation 4, headache 3, asthmatic attacks 2 and periodic anxiety 2. All had symptoms suggestive of allergic disease, 6 being inadequately controlled by hyposensitization therapy.

Since the object of the study was to determine the effect of Pyromen in subpyrexial amounts the dosage schedule was selected accordingly. An initial dose not greater than 0.5 gamma was used.¶ Even without a temperature elevation an occasional patient experienced some untoward reactions, so each dose was gauged by the patient's tolerance to that preceding. Indications of overdosage appeared either as an apparent exacerbation of the original symptoms or as transient drowsiness, muscular aching, faintness, headache, dizziness or nausea

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§Supplied by Baxter Laboratories, Morton Grove, Illinois, through the courtesy of Dr. N. M. Nesset.

¶The material was supplied in ampoules containing 50 gamma per cc. This was diluted to 2 gamma per cc. with normal saline.

occurring within one to four hours after the injection. The dose was not increased if the patient reported any of these. However, during the first three weeks of treatment it was rarely necessary to decrease the dose, as most patients appeared to gain a slight degree of tolerance with each of the first 10 to 12 injections. The average course to which the control group ascribed improvement consisted of 0.5 gamma, 1.0 gamma and 2.0 gamma on three successive days, then 2 gamma 3 times a week for two weeks. After that the interval between doses was determined largely by the patient, who was instructed to return at the first recurrence of symptoms. Individual variability was high, the optimum frequency ranging from 6 times a week (as established by 1 patient) to 1 time in twelve weeks (by 2 patients). The average interval was about four days, but it could not be predicted in individual cases.

Other workers had observed that after an injection of Pyromen, as with ACTH,[12-16, 17, 18] the four-hour white-cell count* was characterized by a leukocytosis with relative lymphopenia and an absolute eosinopenia. Initially, it was presumed that this effect might be used to gauge effective dosage. However, it became apparent that the same hematologic reaction might occur in patients whose symptoms were unimproved or exacerbated as occurred in those who were relieved. Occasionally an intravenous injection of normal saline solution given as a placebo was followed by a drop in eosinophils as great as that produced by the medication, although the percentage of lymphocytes was ordinarily not significantly changed. A severe constitutional reaction was usually followed by a proportionately increased alteration of the hemogram in the direction described. On the other hand, this exaggeration of the usual tendencies was occasionally obtained in the absence of an acute reaction. On the basis of 537 pairs of differential blood counts it was concluded that the hematologic response could not be used to gauge the dosage of the agent.

Objective standards for exact grading of either the severity of those symptoms studied or their response to therapy do not exist. Evaluation therefore rested largely on the subjective impression of the patient. Control periods were introduced at intervals by the substitution of normal saline for several consecutive injections, every detail of the usual procedure being preserved. If a patient failed to recognize a difference when a placebo was substituted for Pyromen, all his reports were considered invalid and his symptoms were recorded as unimproved. The psychiatric status of each subject was evaluated at monthly intervals by his regular therapist. For the purpose of this study grading was limited to 3 categories: *improved*, *unimproved* and *exacerbated*. It was applied to each symptom, not to the patient as a whole.

*Eosinophil counts were made by the method described by Randolph.[14]

Results

Sixty-two patients were treated over a period of seven months with 1621 intravenous injections of Pyromen. The average duration of treatment was seventy-nine days, the average period of observation one hundred and sixty-five days.

Of the 46 subjects that form the basis of this study, 31 were depressed; 15 with recognized allergic diseases were not depressed. The latter group served as "controls," particularly for gauging dosage. Depression was relieved in 23 of the 31. The chief complaint of 12 of the "controls" was alleviated. Depression was relieved in 14 of 17 patients with anxiety tension state; 4 of 4 patients with manic-depressive reactions; 2 of 3 with compulsive-obsessive neurosis; 1 out of 4 diagnosed as schizophrenic; and in each of the single representatives of hysteria, benign depression and psychopathic personality.

All but 1 of the patients who were relieved of depression also had allergic symptoms, which tended to improve in varying degree during treatment. Of the 8 in whom no benefit was observed 2 had seasonal pollinosis, 1 had occasional unexplained localized edema and 3 others had bouts of sneezing not associated with a cold. Those who apparently responded to Pyromen had an average of 10 symptoms each. The subjects who obtained no benefit had an average of 5.25 symptoms. All symptoms tended to respond in the same direction; that is, with unequivocal alleviation of the chief complaint other symptoms tended to be relieved in varying degrees.

In Figure 1 the symptoms reported by all patients are arranged in the order of their incidence. *Anxiety* refers to what the patient describes as "getting all wound up and tense when there's really no good reason for it" or as "the feeling of being terribly worried or frightened without cause." *Fatigue* was recorded only when it occurred despite adequate sleep and could not be relieved by rest. *Bouts of sneezing* were included if they occurred 5 or 6 at a time and were not associated with a developing "cold." The term "*chronic colds*" is used to designate either chronic or frequent episodes of nasal congestion described as "stuffiness" or "sinusitis." *Motor restlessness* is used to cover the sensations described as "having to keep moving" and "legs so jumpy I can't get to sleep." *Memory lapses* (mentioned only in association with major depression — 4 out of 5 with inability to concentrate) were described as episodic phenomena occurring on days when the patient was feeling "groggy" or "punchy." They were not synonymous with "blackouts." The statement by some patients that at times they "felt as if they were in a dream" or that familiar scenes suddenly seemed

"strange and unreal" is summarized by *feelings of unreality*.

The symptoms that tended to abate most promptly were *anxiety*, *depression*, *fatigue* and *insomnia*. The speed of response of upper-respiratory symptoms was variable, some abating within twenty-four hours and others decreasing gradually over several days. No patient who failed to have some alleviation of symptoms within two weeks appeared to derive benefit from continued treatment with Pyromen.

The duration of relief varied from days to weeks. So far as could be determined, it was not correlated with the type of symptom, the speed of the original response, the duration of treatment, the size of the dose or the total amount given. Recurrence of symptoms was usually gradual. In no case did they appear to be more severe after withdrawal of the drug.

Incidental Observations and Comment

Although the study was not designed primarily as an investigation of a new drug, the fact that Pyromen has not yet been completely evaluated seemed to justify including certain pertinent observations on it.

Signs of overdosage were not well recognized until the last two months of the study and may not yet be fully appreciated. In our experience they are of 2 different types, dependent on whether they result from too large a dose or from too frequent administration. Signs of the former have been mentioned in the section on dosage. Approximately 75 per cent of the patients began to have such "reactions" in the third to fourth week of treatment, even though the size of the dose had been the same for several injections. Once this apparent peak of tolerance was attained, it was necessary to decrease the dose to the original amount *or less*. Symptoms that appeared to be due to too frequent administration may represent a cumulative effect or "exhaustion phase." These were initiated by irritability, which usually subsided promptly as the interval between doses was increased. About 25 per cent of patients apparently reached a plateau of maximum benefit that was sustained by a dose of constant size, usually in the order of 3 gamma.

A tendency to increased bleeding on wounding was observed by several patients during Pyromen therapy. Laboratory studies including hemoglobin, red-cell, platelet and reticulocyte counts; bleeding, clotting and prothrombin time; total serum protein; and blood levels of vitamin C, calcium, phosphorus and bilirubin were made on 5 subjects. All were normal. Nevertheless, the observations suggest that Pyromen should be used with caution in the presence of a potentially hemorrhagic lesion such as a peptic ulcer.

The variable hematologic response to the drug might be explained by the normal daily fluctuations in eosinophil percentage in the peripheral blood[19, 20] or might also be in part the result of variations in physical activity and food ingestion, since both of these factors are known to influence the "leukopenic index."[21-25] Neither was controlled in this series.

An occasional patient who had marked relief during a first course of therapy was disappointed in a second course, either because it failed to produce as dramatic improvement as had the first or because it appeared to produce no effect at all.

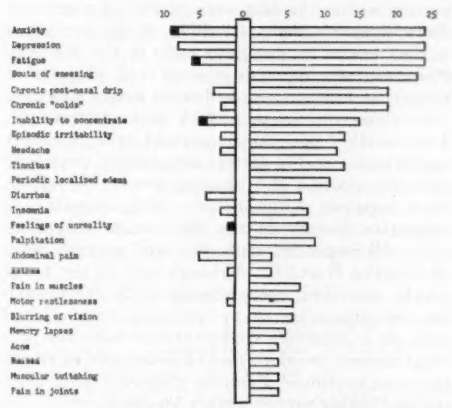

Figure 1. *Symptoms of All Patients in Order of Incidence. The columns at the right of the zero line represent the number of patients in whom the symptom was relieved by treatment with Pyromen; the columns at the left represent those patients in whom the symptom was unrelieved; and the shaded areas indicate exacerbation.*

However, in these cases the patient became so much more accessible during and after the first course that psychotherapy was greatly facilitated.

Two patients whose fatigue was not relieved by Pyromen were found to have mild hypothyroidism, which responded to appropriate treatment. In others, an endocrine factor was probably involved. One twenty-five-year-old student who had not menstruated for five months had a normal period beginning in the second week of treatment and continued to menstruate at twenty-eight-to-thirty-day intervals subsequently. Two young girls for the first time experienced midperiod bleeding for one day. Six others, who had been subject to dysmenorrhea, were relieved while under treatment.

Eight asthmatics were treated. Four were subject to attacks only in the summer and were not under observation at the time when they might have expected respiratory symptoms. Three obtained almost complete relief. The other had her first attack of wheezing while under treatment.

Four cases of severe acne vulgaris cleared while under treatment but began to regress during the second or third week after it was discontinued. One case of seborrheic dermatitis failed to show improvement. A patient with chronic eczematoid dermatitis in acute exacerbation improved rapidly. Since it was already abating slightly at the time treatment was begun, the effect of Pyromen could not be accurately evaluated.

Some of the patients had increased frequency of urination in the first few days of treatment; a few had unaccustomed nocturia for a short time. It was also reported by several that they had lost 3 or 4 pounds within the first week or two of treatment. Since signs of edema (swelling of the eyelids or ankles) tended to disappear early in the course of Pyromen, the apparent diuresis and decrease in weight were attributed to loss of edema fluid.

In about the fourth to fifth week of treatment, 4 ambulatory patients complained of a persistent unpleasant metallic taste; they shortly developed cheilosis, glossitis and bleeding gums. The symptoms appeared simultaneously with anorexia and subjective decrease in the effectiveness of medication. All responded uniformly well to high doses of vitamins B and C. Although each of the 4 was poorly nourished, there was no ready explanation for the appearance of avitaminosis, since all had been on a relatively consistent diet over the previous several months. Two of them suffered recurrences on continued Pyromen treatment when they stopped taking supplementary vitamins.

Ten subjects who had not mentioned fatigue or lack of energy as one of their original complaints repeatedly commented on their increase in energy, as the "lifting of a weight" that they had not known they were carrying until it was relieved. Particularly grateful were the patients who "had forgotten what it was like to feel like getting up in the morning."

Four depressed schizophrenics were treated with Pyromen. The symptoms in 3 patients of remarkably similar personality patterns (exceedingly passive, lethargic persons with homosexual tendencies) were unimproved or exacerbated. Two patients had marked access of energy but with it an increased irritability and agitation. One of them, though able to work for the first time in some weeks, complained that "things were going too fast"; he "couldn't stand it." One appeared unaffected by treatment on three successive days but on the fourth day of treatment appeared more irritable and after his fifth dose was definitely exacerbated, becoming more agitated and depressed, and, for the first time, hallucinating. In marked contrast, the fourth, a more aggressive type, with greater ego strength (and without homosexual tendencies), gradually obtained relief of depression over a period of ten days and has maintained this improvement for over a year. The contrast suggests an inherent physiologic difference between them. Examination of their previous histories and laboratory studies revealed only one dissimilarity that might be significant, namely, that the patient who improved had recognized allergic disease (perennial rhinitis). Although no proof exists that the medication was responsible for either the improvement of one or the exacerbation of the symptoms of the others, we would hesitate to administer Pyromen to another schizophrenic patient who presented the features of the 3 who became worse during treatment.

Not infrequently the severely depressed patient experienced such rapid relief that the observer might question the accuracy of his diagnosis or overestimate the degree of real improvement. One of the first patients to be treated demonstrated this danger.

A twenty-six-year-old girl, a graduate chemist, who was hospitalized, profoundly depressed and retarded, had a remarkable elevation of mood after the first dose of Pyromen. After the second dose she became anxious to return to work and was accordingly discharged to the Out-Patient Department. When she returned for the third dose on the next day she reported progressive improvement and, though not euphoric, appeared calm, smiled spontaneously and was no more retarded than in her best moods She committed suicide on the next day.

It has long been recognized that a patient emerging from a suicidal depression must be protected during the period of transition when he is first freed from his bonds of retardation and agitation, for his manner is deceptive and he may proceed calmly, happily and, in some instances, euphorically to his objective of self-destruction. This patient's dramatic response to the drug appears to have been only a speeding-up of the process experienced in spontaneous recovery from depression. It is our belief, therefore, that the acutely depressed patient should be hospitalized well beyond the time when he first emerges from his depressed state.

The association of certain diseases due to hypersensitivity and accompanied by emotional abnormalities has been observed for a long time. Some neurosurgeons and many allergists have ascribed the psychologic symptoms in certain cases to sensitivity reactions.

Kennedy[26, 27] in 1923 reported 3 cases referred to him because of cerebral symptoms that he believed were due to acute circumscribed edema of the brain. At approximately the same time Bassoe,[28] in a discussion of one of his patients on whom he had performed a decompression, stated that the original diagnosis of brain tumor should have been angioneurotic edema.

Rowe (1930) voiced the opinion that food allergy, — and less often inhalant and bacterial allergy, — might cause headache, nervousness, stupor, disturbances of vision, drowsiness and even con-

vulsions.[29] Since then some other allergists have concurred in the opinion that central-nervous-system symptoms may be manifestations of an allergic state. A composite list drawn from the writings of Coca,[30] Randolph,[31-33] Rinkel,[34] Duke,[35, 36] Clarke[37, 38] and Rowe[29, 39-43] exemplifies the protean nature of the symptomatology observed by them. (The more commonly recognized symptoms are omitted.) This list includes abnormal fatigue, neuralgia, nervousness, irritability, insomnia, asthenia, convulsions, mental disturbances resembling delirium, nightmares, paresthesias, anesthesia, paresis, paralysis, dizziness, tinnitus, blindness, nocturnal restlessness, enuresis and psychotic changes.

In a discussion of behavior problems in children, Randolph[32] points out that the allergic child tends to be sluggish, fatigued, listless and dreamy but may be hyperkinetic, excitable and irritable. Davison[44] corroborates this observation in his enumeration of the evidences of "cerebral allergy": sleepiness on the one hand, insomnia on the other; sluggish thinking, inability to concentrate; childish compulsions; sense of unreality, as if the patient were living in a dream; inability to be pleased about anything; general unhappiness; morbid depression; loss of pride; loss of interest in the other sex. These descriptions suggest a shift in the nervous system from predominantly parasympathetic to sympathetic, as found in certain psychotic patients.[45]

Recent investigation has emphasized the causative role of emotion in allergic reactions. Curry[46] found, however, that only in patients with a history of asthma could an asthmatic attack be produced by mecholyl. Funkenstein states, in his report of a study of the psychophysiologic relation of asthma and urticaria to mental illness, that none of his material would support any theories of causality. He concludes that since the psychologic and physiologic changes go "hand in glove" both are "expressions of the patient's reaction to stress."[45]

The high incidence of allergic symptoms in the patients with depression in this series would seem to substantiate this view. If both psychologic and physiologic reactions are caused by a common agent, Pyromen may act to oppose it. One of our observations, which does not fit in with this explanation, has not been as fully explored as the others. Those nonallergic persons with depression thought to be related to and commensurate with a stress-producing situation derived no apparent benefit from the administration of Pyromen. If further investigation proves this impression to be valid it may indicate that the close association of psychologic and physiologic reactions depends on the common factor of hypersensitivity. A long-term study is in progress to evaluate these features. Tests susceptible to objective interpretation are being included.

Summary

Pyromen, a recently introduced pyrogenic agent, was reported to produce a feeling of well-being when administered in doses sufficient to produce fever. A study was undertaken to determine whether or not this effect could be induced for the relief of depression by subpyrogenic doses of the agent.

Of 62 patients treated, 46 are reported. Fifteen patients with allergic symptoms and without depression served as "controls" for determining dosage. Twelve of these obtained relief. Twenty-three of 31 depressed patients obtained relief. Nineteen of the 23 proved to have allergic symptoms that also were in most instances relieved. In contrast, of 8 depressed patients who had no apparent benefit only 2 had symptoms of allergy.

On the basis of the fact that the psychologic and somatic symptoms of all patients tended to respond alike to Pyromen, it is postulated that the two types of symptoms may be elicited by a common effector agent — and that Pyromen may operate in certain cases to oppose that agent. It is suggested that its failure to mitigate depression not associated with allergic disease may point to sensitization as a potentiating factor in some depressions.

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ANTIBIOTIC SYNERGISM AND ANTAGONISM*

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THE chemotherapeutic armamentarium of the physician has recently grown considerably. The question is no longer merely whether to give penicillin; the choice must now be made among half a dozen or more efficient antimicrobial agents that can be used to advantage in many infectious processes. With the availability of several good drugs the idea naturally arises of using them in combinations rather than singly. It appears reasonable to suppose that if one drug is useful two employed simultaneously should be better and three should ensure the patient's recovery. Considerations of this kind have led to a great increase in the indiscriminate use of mixtures of antibacterial drugs, although little objective evidence has been available on the effect of drug combinations as compared to that of single drugs.

To fill this gap and give better guidance to the practicing physician a number of studies have recently been published by Bigger,[1] Gunnison and others,[2] Hunter,[3] Jawetz and others,[4, 5] Spicer[6] and others, dealing with the effect of drug mixtures on bacteria in vitro. There have been certain discrepancies in the results and conclusions of different investigators — probably due to differences in approach and method. Little would be gained by cataloguing and comparing the findings. It appears more profitable to assess the significance of results obtained in the test tube by applying them to the actual infection, either in a patient or in an experimental animal. This paper presents a summary of our experiences with combinations of antibiotics resulting in synergistic or antagonistic effects in clinical or experimental infections.

Antibiotic Synergism

Most streptococcal infections respond readily to chemotherapy. An exception is formed by the endocarditis or urinary-tract infections caused by *Streptococcus fecalis*. Most strains of this organism are highly resistant to penicillin as well as to other antibiotics, and therapy with single drugs has only rarely resulted in cure. In studying this problem in vitro it was discovered that the possible reason for this behavior was the fact that any single antibiotic, even in optimal concentration, was capable of killing only a certain proportion of the bacterial population. No matter what the concentration of penicillin, some of the bacteria survived in the test tube for long periods of time. Addition of small amounts of streptomycin resulted in a marked increase in the early bactericidal rate of penicillin and in sterilization of the culture. This great increase in the rate of bactericidal action of penicillin

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occurred with concentrations of streptomycin that had no demonstrable effect alone. The combined action consequently appeared to be true synergism (Hunter, 1950; Gunnison and others, 1950; Jawetz and others, 1950).

The in-vitro demonstration of antibiotic synergism was paralleled by combined treatment with penicillin and streptomycin of a significant number of patients suffering from infections with *Streptococcus fecalis*. With this synergistic combination cures were readily obtained (Hunter,[3] 1950; Robbins and Tompsett,[7] 1949).

When antibiotics first became available the majority of staphylococcal infections responded very readily. Yet in the course of the last eight years, — and perhaps as a consequence of the very wide use of these drugs, — most strains of staphylococci have become relatively resistant. The treatment of such infections has consequently become a problem, and cure can often be obtained only if synergistic combinations of antibiotics can be discovered. The following case illustrates this point.

Case Report

Case 1. Mr. M., a 29-year-old Japanese, had undergone in 1949 an operation for resection of a coarctation of the aorta that had produced symptoms and a marked elevation of blood pressure for several years. Some months after the operation he noted the onset of increasing fatigue, with bouts of fever and appearance of red, tender nodules on the ankles. Bacterial endocarditis was suspected; the patient received oral aureomycin, 2 gm. daily, for 2 weeks, followed by penicillin, 800,000 units daily by intramuscular injection, for 4 weeks. He improved temporarily, but soon all symptoms returned, and he entered the hospital of the University of California for study.

Physical examination revealed a well nourished young man with a temperature of 38°C. and a pulse rate of 100 to 120. The blood pressure in both arms was 160 systolic, 50 to 0 diastolic. Findings were typical of coarctation of the aorta and aortic insufficiency and suggestive of bacterial endocarditis.

Blood cultures performed on 6 consecutive days uniformly yielded growth of nonhemolytic, coagulase-negative *Staphylococcus albus*, in an average concentration of 1 to 2 colonies per cc. of blood. Routine sensitivity determinations for a number of antibiotics indicated only temporary suppression of growth of the organism by average concentrations of drugs. The organism was then examined by a technic measuring the killing action of antimicrobial agents (Jawetz and Gunnison, 1950) that has been found helpful in other cases of bacterial endocarditis. The organism was not killed in vitro by penicillin (20 units per cc.), streptomycin (20 microgm. per cc.), chloramphenicol (50 microgm. per cc.), aureomycin (50 microgm. per cc.) or terramycin (20 microgm. per cc.). When combinations of antibiotics were tested in vitro it was found that streptomycin (10 microgm. per cc.) with terramycin (10 microgm. per cc.) was rapidly bactericidal, although the individual components of this mixture had but little effect when used singly. A quantitative demonstration of the antibiotic synergism in vitro is given in Figure 1.

The patient was treated with terramycin, 2 gm. daily intravenously, and streptomycin, 3 to 4 gm. daily intramuscularly. After ten days the therapy was stopped because of severe nausea, vomiting and anorexia and widespread venous thrombosis. All subsequent blood cultures remained negative, the toxicity symptoms cleared promptly and the patient was discharged cured of the infection. When seen 3 months later he was still in good health.

Antibiotic Antagonism

In the course of in-vitro studies on the effects of antibiotic combinations on enterococci (Gunnison and others, 1950; Jawetz and others, 1950), it was observed that chloramphenicol interfered with the bactericidal effect of penicillin, greatly decreasing the rate of bactericidal action. The question arose of the possible occurrence of this phenomenon in vivo.

Groups of white mice were infected intraperitoneally with 100 LD50 (50 per cent lethal doses)

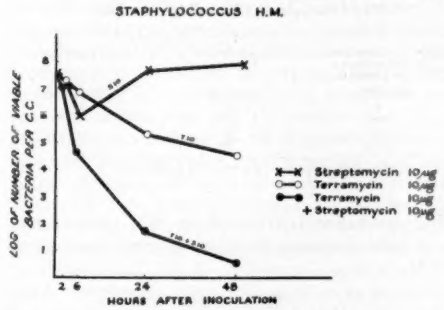

Figure 1. *The Synergistic Action of Terramycin with Streptomycin In Vitro on* Staphyloccus H. M.

of either hemolytic *Streptococcus pyogenes* or *Klebsiella pneumoniae*. At various intervals after infection the animals were given subcutaneous injections of penicillin and intraperitoneal injections of chloramphenicol, terramycin or aureomycin in either single or multiple doses. The death rates in the various treated groups were compared with those of untreated controls. It was uniformly

Table 1. *Cure Rates in Combined Antibiotic Treatment of Mice Infected with* Streptococcus pyogenes.

Quantity Injected (in Addition to 120 Microgm. of Penicillin)	Chloramphenicol	Aureomycin	Terramycin	No Treatment
microgm.	*% of cure*	*% of cure*	*% of cure*	*% of cure*
0	100	100	97.5	0
2.5	—	95	65	—
10	100	40	35	—
25	—	50	60	—
100	66	100	55	—
200	50	—	—	—

*Percentage of cure based on groups of 20 to 40 mice.

found that the addition of any one of the three "newer antibiotics" to penicillin greatly diminished the cure rate obtainable with penicillin alone. A few selected results of these studies are presented in the following tables.

The degree of interference with the therapeutic action of penicillin varies with the drug and the dose.

Interference is maximal when relatively ineffective doses of aureomycin, chloramphenicol or terramycin (curing alone less than 30 per cent of animals) are added to doses of penicillin that alone cure 70 per cent or more of animals. The antagonism becomes less as the dose of "interfering drug" increases to the point of being curative by itself. The type of antagonism illustrated in the tables occurs with either single or multiple doses of the drugs, given early or late in the infection, simultaneously or at different times, with certain limits. The possible mechanisms involved in this phenomenon have been discussed elsewhere (Jawetz and others, 1951).

TABLE 2. *Cure Rates in Combined Antibiotic Treatment of Mice Infected with* Klebsiella pneumoniae.*

Quantity Injected (In Addition to 6 Mg. of Penicillin)	Aureomycin	No Treatment
micrgm.	*% of cure*	*% of cure*
0	82	0
10	35	—
50	40	—
200	70	—

*Percentage of cure based on groups of 20 to 40 mice.

Discussion

The judicious employment of antibiotic combinations permits the cure of infections that cannot otherwise be attacked. It has been demonstrated that the laboratory may guide the clinician by proper examinations in the simultaneous use of multiple chemotherapeutic agents and lead him to success. We have found that laboratory tests for "antibiotic sensitivity" of micro-organisms that are based entirely on the development of turbidity in broth may be misleading, particularly in conditions such as endocarditis, in which actual killing of bacteria is of paramount importance. The most useful laboratory test in our experience, giving the most reliable correlation with clinical results, is one in which the bactericidal action of drugs is estimated. The bactericidal rate may be measured, by means of subcultures or plate counts, from broth tubes in which large bacterial populations are exposed to single or multiple drugs. This permits the selection of the drug or combination of drugs that has the most rapid as well as the most lethal effect on the micro-organisms.

We agree with Bigger's (1950) conclusion that the "synergism . . . might be of considerable value . . ."; we are uncertain, however, about the second half of his conclusions: ". . . the antagonism which has been demonstrated in a few cases is very unlikely ever to represent a real danger." It is true that the antibiotic antagonism described in this paper is essentially an interference with the therapeutic action of penicillin by aureomycin, chloramphenicol or terramycin — not the reverse. The interference results only in quantitative reduction of therapeutic efficacy and can be overcome by a large excess of any of the drugs involved. For these reasons the clinical significance of the phenomenon of antibiotic antagonism observed in experimental animals cannot be clearly assessed at this time. We believe, however, that an awareness of the possibility of antagonism between chemotherapeutic agents might induce physicians to be on guard for such occurrences in patients. Similar considerations might promote the scientific use of antimicrobial agents. These invaluable drugs should not be dispensed indiscriminately but should be prescribed only when properly indicated. One should refrain from the arbitrary simultaneous use of several antimicrobial agents unless the efficacy of the combination is well established clinically or its use is indicated on the basis of thorough laboratory tests.

Conclusions

The availability of several effective antimicrobial agents has promoted their indiscriminate use. Certain microbial infections no longer respond to therapy with a single drug, and the use of drug combinations must be considered.

In such cases advantage may be taken of the synergistic effect of certain combinations of chemotherapeutic drugs. Antibiotic mixtures should not be administered haphazardly, but their use should be based on etiologic diagnosis and, — whenever possible, — a test-tube evaluation by proper laboratory methods.

Although antibiotic synergism will permit cure of certain infections, the administration of arbitrary mixtures of chemotherapeutic agents cannot be recommended, as antagonism between certain drugs has been demonstrated in vitro as well as in experimental infections of mice. Careful clinical observation will be necessary to establish the significance of antibiotic antagonism in the treatment of human disease.

Addendum

Since this paper was written a convincing series of cases of antibiotic antagonism seen in clinical practice has been reported by Lepper and Dowling.[8]

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MULTIPLE MYELOMA*

A Report of Four Cases Demonstrating Bence–Jones Proteinemia Found during Routine Complement-Fixation Tests

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BENCE–JONES protein in the serum, sufficient to produce a visible precipitate at 56°C., is of rare occurrence. Review of the literature discloses no more than 20 such cases recorded since the initial report of this finding by Ellinger[1] in 1899. Only 4 instances of serum precipitating at the 56°C. temperature utilized to inactivate the serum complement have been recorded in over 700,000 complement-fixation studies made in the serology laboratories of the Cleveland Clinic since its founding in 1921. During this time 162 cases of multiple myeloma have been observed in the Cleveland Clinic and the Cleveland Clinic Hospital.

Apparently no relation exists between the hyperglobulinemia and either the presence of Bence–Jones protein in the serum or its concentration in the urine.[2-5] It is generally accepted that approximately 65 per cent of persons with multiple myeloma excrete Bence–Jones protein in the urine, and only about 16 per cent of the patients with this malady have a demonstrable hyperproteinemia at any time during the course of their disease. Serum studies conducted by the electrophoretic and ultracentrifugal technics have borne out this earlier observation of the lack of relation between the presence of Bence–Jones protein in either urine or serum and the often-noted hyperproteinemia.[6, 7] It is now accepted that the increment in the serum-protein content in the majority of cases showing hyperglobulinemia is not due to the presence in the serum of the Bence–Jones protein.[8]

The difficulty encountered in adequate laboratory studies of Bence–Jones protein has been sufficiently described in numerous studies. Perhaps the basis of this difficulty lies in the fact that the term "Bence–Jones protein" refers to an ill-defined group of proteins, the precise physical and chemical properties of which have never been completely explored. Certain groups of investigators have regarded this protein as representing a number of structures differing in their physical, chemical and immunologic properties; other investigators have considered the Bence–Jones protein to represent one entity. Current investigations in the serology laboratories of the Cleveland Clinic point to the immunologic identity of Bence–Jones protein derived from the different patients. The protein substances investigated were obtained from both urine and serum.

Electrophoretic, ultracentrifugal and immunologic studies, because of their complexity, are all supplementary aids in the diagnosis of multiple myeloma and cannot at the present time be regarded as supplanting the older technic of demonstrating Bence–Jones protein in the urine or serum. The high cost to the patient of these investigative procedures also precludes their routine use. Currently none of these procedures can be used in the diagnostic screening but must be reserved for confirmation of a suspected diagnosis. Because of the fact that in most clinics serologic tests for syphilis are routine, the heat test for the presence of Bence–Jones protein in the serum remains of great importance, since it is done incidentally in the course of inactivating the serum complement. The four cases to be presented are cases in which the first positive indication of the diagnosis was obtained during the initial diagnostic procedures in which precipitates were reported as occurring when the serum was heated to 56°C. to inactivate the complement incidental to the performance of the Kolmer[9] modification of the Wassermann complement-fixation test for syphilis.

CASE REPORTS

CASE 1 (No. 228-123). The first observation in this clinic of coagulation of serum at 56°C. was made on a 64-year-old male patient first seen on June 23, 1930. At that time he had had pain and stiffness in numerous parts of his body for one year. The pain was of varying intensity and usually regressed within one to two weeks. However, for 2 weeks prior to hospitalization he had complained of constant stiffness and pain in the lower back, radiating bilaterally around to the midhypogastric region. The only positive finding in the family history, past history and systemic review was a weight loss of 7 pounds over the 4-month period preceding hospitalization.

Tenderness in the 10th right intercostal space in the midaxillary line and tenderness with limitation of motion of the left shoulder were demonstrated on physical examination. Lumbar spasm without localized tenderness was observed; there was marked bilateral restriction on the straight-leg-raising test. The prostate was found to be slightly boggy and somewhat enlarged. Other findings at physical examination were within normal limits.

The admission laboratory studies showed an erythrocyte count of 3,240,000, with a hemoglobin of 11.5 gm. The total leukocyte count was 5400 with a normal differential. The serologic test for syphilis was not reported, since the serum coagulated at 56°C. Roentgen studies, at this time limited to the lumbar spine, were interpreted as consistent with the diagnosis of hypertrophic arthritis.

The anemia became progressively more profound and the patient's clinical course was a rapid downhill one, characterized by the development of back and chest pain not relieved by immobilization and heat. A roentgen examination of the dorsal spine 15 days before the patient's death dis-

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closed a compression of the tenth dorsal vertebra, "possibly a malignancy of metastatic origin." A biopsy of the right 12th rib performed on the following day was interpreted as showing hyperplasia of the bone marrow. After this operative procedure the patient suffered numerous fractures of the ribs and developed bilateral lower-lobe pneumonia, dying on November 25, 1930. Post-mortem examination disclosed neoplastic invasion of the marrow, the microscopical sections of which were consistent with the diagnosis of multiple myeloma.

CASE 2 (No. 316-207). A 53-year-old man was first seen on September 12, 1938, at which time his complaints were all relative to the anemia for which he was referred. For five months prior to admission he had noted increasing dyspnea and weakness, with severe lower-back pain radiating down the right flank. Nine transfusions of 500 cc. each of whole blood during this period had failed to correct the anemia. The family history and past history were noncontributory; systemic review disclosed a history of intolerance to fatty foods of several years' duration, accompanied by constipation. For the 5-month period preceding hospitalization the patient had noted nocturia of increasing amount and frequency. Physical examination on admission demonstrated a pale, poorly nourished, wasted man whose gingival tissues were discolored by a heavy metal line, which was presumed to have been caused by bismuth administered some years ago during treatment for syphilis. Hepatomegaly and splenomegaly were prominent features of the physical examination, which was otherwise thought to be within normal limits. The erythrocyte count at this time was noted to be 1,300,000, with a hemoglobin of 3.5 gm. A normal differential white-cell count was observed, with a total leukocyte count of 14,050. The serum coagulated at 56°C., and Bence–Jones protein was reported as present in the urine. Bone marrow obtained by sternal puncture showed a morphologic picture consistent with that of multiple myeloma. Roentgen study of the skull disclosed sellar enlargement, with erosion of the posterior clinoid processes. An area of osteoporosis was seen in a film of the 4th right rib. The clinical impression was multiple myeloma. The patient was given deep roentgen therapy and multiple transfusions but died on the 9th hospital day.

CASE 3 (No. 420-602). A 64-year-old man entered the hospital on March 24, 1944, with a complaint of back pain dating from an injury to his back 3 months prior to hospitalization. The exact nature of the injury is not stated in the chart. The back pain originated in the lumbar region and radiated bilaterally to the abdomen. A weight loss of 32 lb. was noted in the 2-month period preceding hospitalization. The family history, past history and the balance of the systemic review showed no relation to the patient's illness. The patient was found to be slight, pale and poorly nourished, but other significant findings were not noted in the physical examination. A serum precipitate was observed after the serum had been incubated for 30 minutes at 56°C. The erythrocyte count was recorded as 3,260,000, with a hemoglobin of 9.7 gm.; the total leukocyte count was recorded as 6200. The clinical impression on admission, — hypertrophic arthritis, — was substantiated by roentgen studies of the spine. Shortly thereafter, however, the working diagnosis was changed to that of cancer, metastatic to the spine. The patient's condition became rapidly worse, and on the basis of his clinical picture and roentgen studies the diagnosis of multiple myeloma was established. He died 1 week later on July 26, 1944.

CASE 4 (No. 619-972). A 57-year-old pottery worker presented himself on October 19, 1950, with a 3-week history of vomiting that usually occurred after eating. Pain in the right upper quadrant of sufficient severity to awaken the patient at night was not alleviated by food. Indigestion, relieved by sodium bicarbonate, had been noted for 9 months prior to the development of the acute gastric complaints. Coexistent with the indigestion had been "rheumatic pains," intermittent in nature, located in the lumbar region and occasionally radiating down the right flank to the right groin. A 30-pound weight loss had been noted over this 10-month period. Headaches, increasing in severity and frequency, had been noted for 4 months prior to hospitalization, and nocturia, 3 to 4 times nightly, without accompanying diurnal frequency, had been a feature of the present illness. Physical examination of this well developed, well nourished, slightly pallid man, on whom the referring physician had made the clinical and radiologic diagnosis of duodenal ulcer, failed to demonstrate many findings of significance. Deep palpation of the right upper quadrant produced slight muscle guard. The prostate was firm and slightly enlarged. Other physical findings were within normal limits. The erythrocyte count was 3,360,000; both red and white blood cells were normal on smear. The total leukocyte count was 10,250. The serum of the patient, when incubated at 56°C., coagulated into an almost solid gel. Microscopical hematuria and pyuria were observed in the urine, in which the specific gravity was 1.010 and the tests for Bence–Jones protein were negative. Positive immunologic tests, the technic for which is the subject of a report[10] now in press, were reported on these urine samples, the chemical tests of which failed to demonstrate the presence of this abnormal constituent. However, Bence–Jones protein was demonstrated by the salting-out technic on urine obtained on the patient's 7th hospital day. The positive radiologic findings were of a constant duodenal bulbar deformity believed to be an ulcer crater and of radiolucent areas in the calvarium suggestive of multiple myeloma. After the diagnosis of multiple myeloma had been established by sternal-marrow aspiration, the clinical efforts were unsuccessfully directed toward relief of the azotemia and control of the persistent vomiting. The patient's clinical condition became progressively less satisfactory. He was discharged on his 25th hospital day. His physician later reported that the patient died of uremia about 4 months after discharge.

DISCUSSION

The four cases presented were similar in many respects. They represent essentially the same age group, varying from fifty-three to sixty-four years of age. The series is too small to lend significance to the survival time dating from admission to the hospital, but it is of interest that none of the patients showing Bence–Jones protein in the serum survived longer than 181 days from the date on which they were first seen. The grave prognostic implication of the finding of Bence–Jones protein in the serum is thus apparent. All the patients described symptoms that in retrospect could be regarded as representing skeletal involvement. The radiologic findings in all these cases were consistent with those of multiple myeloma. The hematologic picture in all cases was compatible with multiple myeloma, but of even greater and more obvious significance was the finding of Bence–Jones protein in the serum.

Sternal-marrow aspiration was performed on 2 patients; in each the morphologic picture was consistent with that of multiple myeloma. One of these was carried out in 1938, the other in 1950. Since the technic involving smears of the bone marrow obtained by aspiration was described by Arinkin[11] in 1929 and was not widely used for a few years thereafter, it was not available for use in the first case. The fixed marrow sections obtained from the first patient were interpreted as showing hyperplasia of the bone marrow. Recent review of these sections, which were made in 1930, was regarded as consistent with the diagnosis of multiple myeloma and served to re-emphasize the fact that marrow biopsies, of whatever type, are in reality random samples. Although it would have been desirable to have an aspiration smear for study, many investigators, notably Peabody,[12] have

thought that this technic is not superior to that of study of the fixed marrow sections. More recent workers in the field of hematology, however, have emphasized the importance of smears obtained by the aspiration technic in cytologic and morphologic diagnosis.

From the point of view of the clinical pathologist, the finding of Bence–Jones protein in the serum is so rare, and its correlation with multiple myeloma so high, that this positive finding imposes on the clinician the burden of proving that the disease in question is not multiple myeloma. In three of the four cases here presented this finding, so highly suggestive of multiple myeloma, was overlooked. In the last case, the presumptive diagnosis was made on the basis of this finding, which was corroborated by serologic tests on the urine, marrow-aspiration studies and radiologic findings. In two of these cases the final diagnosis was not attained until just prior to death; in one the diagnosis was not made until autopsy was performed. This is unfortunate from the academic standpoint, since all these cases presented two of the cardinal features of multiple myeloma, namely, persistent anemia and Bence–Jones protein in the serum.

Summary

In 4 cases, in over 700,000 complement-fixation tests made at the Cleveland Clinic, a precipitate has been observed during inactivation of the serum at 56°C. All these patients were later shown to have multiple myeloma. Emphasis is laid on this simple heat test of serum, made routinely during inactivation of serum complement, as a diagnostic aid in finding Bence–Jones proteinemia. Clinical abstracts are presented of these four cases with Bence–Jones proteinemia demonstrable by heat. Current studies strongly suggest immunologic specificity of the Bence–Jones protein. Immunologic tests for Bence–Jones protein in the urine are of considerable value in those cases in which such protein cannot be demonstrated by chemical tests.

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MEDICAL PROGRESS

ACTH AND CORTISONE IN THE TREATMENT OF OCULAR DISEASE

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OPHTHALMOLOGY has witnessed a widespread clinical trial of cortisone and adrenocorticotrophic hormone (ACTH) during the past two years, and the results have opened an entirely new approach to the treatment of certain ophthalmologic conditions. At present, although the number of publications on the subject is not extensive, it seems appropriate to review the available literature and to call attention to the current concepts of both etiology and therapy that have emerged from the use of these agents, particularly in the inflammatory ocular lesions. It was apparent initially that considerable enthusiasm was to be associated with the early experiences; although more time will be required before a final appraisal is possible, a periodic evaluation of these new agents will facilitate the establishment of their proper place in ophthalmology.

HISTORICAL REVIEW

Vail,[1] writing editorially in the *American Journal of Ophthalmology* for October, 1949, was the first to suggest the possible clinical value of ACTH in ocular disease. The earliest record of the use of ACTH in ophthalmology appeared in the *Proceedings of the First Clinical ACTH Conference*,[2] in which acute iritis and interstitial keratitis were listed among those diseases in which the hormone showed clinical promise.

The attention of ophthalmologists was initially drawn to the use of ACTH in eye diseases by a paper of Gordon and McLean,[3] presented before the Eastern Section of the Society of Research in Ophthalmology in January, 1950. Earlier in the fall of 1949, these authors and, independently, Olson and his co-workers[4] had begun a simultaneous evaluation of the efficacy of ACTH in ocular disease; their preliminary reports were published concurrently in April, 1950. Gordon and McLean[3] had studied the effects of the hormone in 6 cases, only 3 of which showed inflammatory lesions. The investigation of Olson and others[4] was concerned with the effects of ACTH in the acute nonspecific inflammatory lesions; favorable results in 7 cases were reported. Prior to these publications, Mann and Markson[5] reported on the successful use of ACTH in a rheumatoid patient with associated iritis and episcleritis. Blake and his co-workers[6] recorded the failure of ACTH to improve primary glaucoma in a report of August, 1950. Harvey and his co-workers[7] were perhaps the first to study the effect of ACTH in a patient with ocular inflammatory disease, having used the drug as early as September, 1949. Their report, however, was not forthcoming until November, 1950. Directly prior to this, Woods[8] recorded his experiences with the pituitary hormone in a study that was initiated early that year; his report included 5 cases that were later presented in Harvey's paper. In December, 1950, Gordon and others[9] and Olson and his co-workers[10] reviewed their first year of experience with ACTH in ophthalmology at the second Clinical ACTH Conference; the results reported were essentially like those described in this general review of the clinical studies.

The early clinical experiences with cortisone in general paralleled those with ACTH. The corticosteroid has received an extensive therapeutic trial, but the results remain, for the most part, unpublished. Its efficacy in ocular inflammatory disease was recorded first by Steffensen and others[11] in July, 1950. In this preliminary paper mention was made of the therapeutic value of cortisone, not only by parenteral administration but by topical application as well. This was confirmed later by Woods[8] and by Harvey and others[7] in their reports. Henderson and Hollenhorst[12] in September, 1950, presented their results with parenterally administered cortisone in 8 cases of inflammatory and allergic eye diseases. In March, 1951, there appeared simultaneously a series of excellent articles covering the results of treatment with both ACTH and cortisone in a variety of ocular diseases.[13-19] These reports generally confirmed the original impressions of the earlier investigators mentioned above; the results have been incorporated in this review.

CLINICAL RESULTS

Certain limitations of interpretation must of necessity be accepted. This is partly due to the fact that uniform criteria have not been employed by the several authors in appraising their therapeutic results. In some cases interpretation of results has been objective and based on changes in the pathologic process, whereas in other instances improvement has been judged subjectively — as in the visual acuity. Here, failure to demonstrate improvement in the latter does not neces-

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sarily mean a poor result, for favorable alterations may have been effected in the basic pathologic process. In the review of the literature, moreover, considerable variation in dosage and duration of treatment has been noted, a fact that undoubtedly complicates the appraisal of results. This is true particularly in the more chronic lesions when the pathologic process is not accessible to direct observation. In other cases, failure adequately to differentiate an acute and a chronic lesion has led to further difficulty in evaluating the over-all therapeutic benefits. This distinction has considerable importance in view of the generally more favorable results observed in the acute inflammatory lesions. Since standard criteria for judging the value of agents have not been established in ocular therapeusis, one must often employ such relative and questionably desirable terms as "improved," "favorable," "satisfactory" and so forth. It has, accordingly, been necessary to use some freedom of interpretation in including the results herein reported, and it would be manifestly inappropriate to speak in terms of percentage results in the studies that have accumulated to date.

The early reports of Gordon and McLean[3] and of Olson and others[4] made no claims concerning the general usefulness of ACTH and cortisone in ophthalmology, primarily because too few cases had been treated and the duration of observation had been too limited. It was initially apparent that rapid resolution of an acute nonspecific inflammatory eye lesion could be achieved with the parenterally administered hormones, and the continued good results, as reported in the more recent articles, have in no way modified the earlier impressions. Thus, Olson and others,[13] in treating 23 cases of acute nonspecific inflammatory diseases, including iridocyclitis, chorioretinitis, retinitis centralis and diffuse uveitis, failed to achieve continued remissions in only 3 patients. Gordon, McLean and Koteen,[9] in their recent review, reported generally similar experiences, but, judging from their tabulations, it is difficult to separate the acute from the chronic lesions. Thus, interpretation of their over-all results in the acute group alone is limited. However, they state that nearly all their favorable responses in patients with choroiditis, iridocyclitis and optic and retrobulbar neuritis were seen in the acute lesions of short duration. Fitzgerald and others[16] obtained good results in 11 of 13 patients with acute nongranulomatous uveitis treated with parenterally given hormones, and similar favorable responses were seen in 9 of 16 patients treated systemically for acute granulomatous uveitis. In the group of patients with acute posterior lesions, including choroiditis and chorioretinitis, they obtained satisfactory improvement in 15 of 17 patients treated with the parenterally given hormones.

Variable results have been encountered in acute optic neuritis. Gordon and others,[9] using ACTH in the treatment of 7 patients, obtained improvement in 6, one of whom later relapsed. Olson and others[13] treated 2 cases with parenterally given cortisone and 1 with ACTH; all showed complete remission. Scheie and others,[14] on the other hand, reported questionable improvement in 2 cases treated with ACTH. In treating retrobulbar neuritis with ACTH, Gordon and his co-workers[9] noted improvement in 5 of 6 patients. Leopold and others,[19] using cortisone in 4 such patients, observed transient improvement in only 1. Scheie[14] treated 1 patient with cortisone and 1 with ACTH; both showed questionable improvement. In the case reported by Fitzgerald and others[16] no improvement was noted, but treatment with minimal amounts of ACTH may have contributed to the failure.

Koff and his co-workers[20] and Steffensen and others,[17] using the subconjunctival and topical routes respectively, have demonstrated the effectiveness of locally applied cortisone in the resolution of the milder forms of acute nonspecific inflammatory disease in the anterior segment of the eye. The subsequent reports of Mosher,[15] Leopold and his co-workers[19] and Fitzgerald and others[16] confirmed the earlier work and demonstrated the unquestioned efficacy of local administration of cortisone in a large number of patients with this type of ocular lesion.

In summary, it can be said without reservation that the two hormones are now replacing rapidly the long-established foreign-protein therapy in acute nonspecific inflammatory diseases of the eye. The rapidity of response and the resultant brief duration of therapy have given rise to few if any limitations. There appears to be general agreement on this among those who have reported their results so far. The discrepant results in acute optic neuritis and retrobulbar neuritis probably stem from differences in dosage, duration of treatment, route of administration and acuteness of the presenting lesion.

The therapeutic benefits of the use of these hormonal agents in the treatment of chronic nonspecific eye lesions have not been so readily apparent. Certainly, one can say that the number of patients who have remained in remission after the initial course of therapy with either ACTH or cortisone has been small. The over-all results as reported by Olson and others[13] in the treatment of chronic nonspecific eye lesions were not encouraging, although it was believed without question that the "active" features of the chronic lesions were often controlled during the period of therapy. A similar conclusion was reached by Scheie and others[14] in the treatment of 4 patients with chronic diffuse granulomatous uveitis. Fitzgerald and his co-workers[16] appear to have achieved better results than other workers in treating the chronic lesions. They have reported improvement in 11 of 15 patients treated locally with cortisone for chronic

nongranulomatous anterior uveitis. Surprisingly favorable results were obtained in 14 patients with chronic granulomatous anterior uveitis. In this series, 4 were improved of 6 treated systemically with hormones and 4 were improved of 8 treated locally with cortisone. In patients with chronic posterior uveitis and chorioretinitis, however, the results were not encouraging; only 2 of 11 patients were considered to have recovered. In the group, as noted by both Olson[13] and Scheie,[14] 5 patients showed temporary improvement but relapsed when treatment was withdrawn. The last-named investigators reported failures in all of 12 cases in which chronic granulomatous posterior uveitis was treated locally with cortisone. Thus, the results in the chronic inflammatory ocular lesions have paralleled, in a sense, those obtained in patients with other chronic inflammatory lesions such as long-standing rheumatoid arthritis, in which early relapses have been common after cessation of treatment.

The response to ACTH and cortisone in a number of other inflammatory eye lesions has been the subject of extensive investigation. Olson and others[13] have reported that both ACTH and parenterally given cortisone are effective in the treatment of sympathetic ophthalmia; Woods[8] has demonstrated a similar favorable response to topical treatment with cortisone alone. Fitzgerald and others[16] obtained good results in 2 of 5 patients treated with ACTH for the same lesion. Leopold and his co-workers,[19] using cortisone subconjunctivally, observed improvement in 2 patients, and Mosher[15] obtained similar responses in 3 patients when cortisone was used as a collyrium. Mosher noted no improvement in 2 patients when the cortisone was used subconjunctivally. It is understood, however, that sympathetic ophthalmia is often a presumptive diagnosis that may lead to some difficulty in reporting specific results. To date, only 4 well-documented cases have been reported in which histologic study has proved the diagnosis. Of these, 3 have been patients of Fitzgerald and his co-workers,[16] 2 of whom showed improvement during ACTH therapy and only 1 continued without relapse. In the fourth patient, reported by Gordon and others,[9] several remissions were effected by hormonal therapy but relapses occurred when treatment was withdrawn.

Steffensen and his co-workers[11] early reported the favorable influence of first ACTH and then topical cortisone in 1 patient with syphilitic interstitial keratitis. A similar result was subsequently achieved when locally administered cortisone alone was employed.[21] More recent reports of the hormonal treatment of this disease have not presented uniform results. Scheie and others[14] successfully treated 2 of 3 patients with ACTH; 2 other patients had remissions with locally given cortisone alone. Fitzgerald and others,[16] in contrast, had 1 patient who was unimproved on both ACTH and cortisone; Leopold and his co-workers[19] obtained poor results in 4 patients treated with subconjunctivally administered cortisone. Control of this lesion with ACTH or cortisone is possible evidence of its hypersensitivity etiology and arouses curiosity concerning why subconjunctivally given penicillin should be effective, as observed previously by Steffensen[21] in 5 patients.

Other ocular diseases of probable allergic origin have been treated with these newer hormonal agents; in some cases favorable results have been obtained. Erythema multiforme with ocular involvement has been shown by Olson and others[13] to undergo rapid and complete remission without complications, although antibiotics were necessary for the control of secondary infections. Bleier and Schwartz[22] demonstrated a dramatic response to parenterally given cortisone in a patient with erythema multiforme. The studies of Leopold and others,[19] using subconjunctivally and topically given cortisone in 1 patient, and those of Scheie and others,[14] using cortisone drops alone in 2 cases, were without favorable results. This suggests, perhaps, that parenteral administration of cortisone is necessary to achieve control of this disease.

Vernal conjunctivitis has been shown by Olson and others[13] to regress markedly during the period of parenteral hormonal therapy, but early relapse has taken place after cessation of treatment. Similar results were obtained in this condition by Henderson and Hollenhorst,[12] using parenterally administered cortisone. Leopold and others[19] reported improvement in 3 of 6 patients treated with cortisone drops. Comparable responses were reported by Scheie and others[14] in 6 cases treated with cortisone; Mosher[15] obtained similar results in 1 patient. In our experience, the cortisone ointment has proved somewhat superior to the cortisone drops, but further experience with the ointment is necessary. Permanent control of this lesion appears highly unlikely in view of its hypersensitivity etiology.

Phlyctenular keratoconjunctivitis has been reported by Steffensen and others[17] to be controlled effectively by topically given cortisone. The largest series of patients with this entity was presented by Thygeson and Fritz,[18] who obtained good results in 14 patients treated with either topically or subconjunctivally administered cortisone. In a later series of 12, they achieved remissions in 11 patients similarly treated.[18] Equally favorable results were recorded by Scheie and others[14] and Fitzgerald and his co-workers,[16] whereas Leopold and others[19] reported 1 patient whose condition was unimproved after subconjunctival administration of cortisone. It is not too early to say that the hormonal treatment of this ocular lesion has led to almost uniform success; locally given cortisone appears to be the treatment of choice.

Although Steffensen and his group[17] have reported only 1 patient with tuberculous keratitis who responded favorably to locally given cortisone, our experiences with 4 additional patients have been similar. Leopold and others,[19] using subconjunctivally administered cortisone, demonstrated improvement in a patient with the same ocular lesion. The former investigators are of the opinion that the hormone-induced remissions may not be sustained and that relapses will occur sooner or later. Uniform success in the control of the relapse, however, has justified the opinion that it will remain the most effective therapeutic procedure. This does not obviate the need for tuberculous desensitization, which in some cases may lead to a longer remission. Woods[8] and Mosher,[15] using topically administered cortisone, have reported excellent results in the treatment of sclerokeratitis. This lesion may be identical to tuberculous keratitis and is mentioned here with this consideration in mind.

Locally given cortisone has induced remissions in 3 patients with acne rosacea keratitis as demonstrated in the reports of Fitzgerald and others[16] and Steffensen and others,[17] but the number of cases is too small to warrant any further comment.

Marginal corneal ulcers, considered by many to be allergic in origin, have been found to respond effectively to cortisone. Leopold and others[19] obtained remissions in 3 patients treated with subconjunctivally administered cortisone, and Fitzgerald and his co-workers[16] and Mosher[15] each have reported 1 case improved on cortisone drops.

Scheie and others[14] reported that 5 of 6 cases of nonspecific marginal keratitis responded to the topical instillation of cortisone drops. Two patients with nonspecific keratitis profunda and 2 with nonspecific superficial keratitis were reported by Steffensen and his group[17] as responding favorably to topically instilled cortisone. Leopold and his co-workers[19] observed a similar response of the latter lesion in 1 of 2 cases. Scheie and others[14] listed a good result in 1 patient with keratitis profunda treated with the topical instillation of cortisone. Undoubtedly, other cases of either deep or superficial nonspecific keratitis have been reported as improved, but because of differences in terminology and differences of opinion among the various authors concerning etiology, proper evaluation is somewhat difficult. The treatment of choice, however, is locally given cortisone, as the results above strongly suggest.

In the treatment of episcleritis, uniformly favorable results have been obtained by all authors. Fitzgerald and others[16] used ACTH in 2 patients and topically given cortisone in 8 and obtained improvement in all. Scheie and others[14] likewise reported remissions in 3 cases treated with topical cortisone. This particular ocular disease may well be included in the group of acute nonspecific inflammatory lesions mentioned above but is considered separately in accord with the classifications generally employed.

During the topical administration of cortisone in 2 cases of dendritic ulcer, Steffensen and others[17] observed relief of pain and reduction in vascularity of the lesion, but these changes were not considered indicative of improvement in the true sense of the word. Fitzgerald and others[16] reported 4 patients treated locally with cortisone as improved, as did Leopold and others[19] in a similar number of patients treated with subconjunctivally instilled cortisone. The latter authors pointed out that the time factor alone may have been highly important in the attainment of the favorable results that appeared to occur during cortisone therapy. Scheie and his co-workers[14] reported on the topical cortisone treatment of 2 patients and claimed that healing did not take place in one.

Olson and others[13] have reported the successful use of ACTH in 1 patient with herpes zoster ophthalmicus in whom a permanent remission followed the subsequent local use of cortisone. Leopold and others[19] used cortisone subconjunctivally in 3 patients and observed that 2 relapsed and 1 improved. Fitzgerald and others[16] reported improvement in 1 patient receiving cortisone topically.

In a patient with ocular pemphigus no improvement was observed by Leopold and others,[19] who used both the subconjunctival injection and topical instillation of cortisone. Fitzgerald and others[16] had a similar experience with topically given cortisone in 1 case; in the more recent studies of Olson,[23] favorable symptomatic control has been achieved with the same preparation. Marked improvement of the acute inflammation and regression of the lymphoid overgrowth was reported by Woods[8] when cortisone was used locally in a patient with possible ocular pemphigus. Little in the way of conclusions can be derived from the limited information to date available on the hormonal treatment of these last two ocular diseases.

Retrolental fibroplasia has been the subject of study by several authors; so far, the results conflict somewhat. Reese and Blodi,[24] in the largest series reported to date, have described results in 14 patients treated with ACTH. In all patients the process was arrested or was observed to regress; where treatment was started early, the retrolental membrane failed to develop. Contrary findings were reported by Fitzgerald and others[16] in observations on 6 patients, 3 of whom were treated topically with cortisone. No improvement was observed, but only the 3 treated with ACTH can be properly compared with the series mentioned above. Scheie and others[14] studied 5 patients with retrolental fibroplasia but thought that results in only 2 could be evaluated properly. Of these, the one treated with ACTH showed results that they thought justified further investigation. Gordon and others[9] reported 4 failures in 5 patients treated with ACTH.

Our experiences to date, though limited, suggest that patients with this disease should receive hormonal therapy parenterally at the earliest possible stage. Again, it is suggestive that some of the discrepancies in the results may stem in part from the fact that several observers have begun the treatment at different times in the evolution of the disease.

In their studies of patients with retinitis pigmentosa, both Steffensen and Kukora[25] and Gordon and others[9] have found temporary improvement to occur during treatment with either ACTH or parenterally given cortisone. In all patients, however, early relapses have occurred, and neither drug appears to have great clinical usefulness in the treatment of this disease. Steffensen and Kukora,[25] in their critical study of 14 patients, found that ACTH was more effective than cortisone in increasing retinal sensitivity, as measured by the biophotometer. In their investigation, which was concerned primarily with the melanophore hormone, they observed that it was inferior to both ACTH and cortisone in enhancing the subnormal photosensitivity of patients with this disease.

In such lesions as senile macular degeneration and juvenile macular degeneration, only Woods has reported improvement to date. His single case of senile macular degeneration was treated with 2228 mg. of ACTH over a period of 47 days. In view of the lengthy treatment of this essentially noninflammatory lesion, it is difficult to evaluate the result. Fitzgerald and others[16] made observations on 7 patients; Leopold and others[19] studied 2; Olson and others[13] studied 1; in all cases no improvement was observed. In our unpublished results, 5 patients with macular degenerative lesions have failed to show any sustained response to either hormone; when improvement was observed, it appeared to parallel temporary reduction in the associated subretinal edema. It is difficult to visualize any other basis of response in degenerative retinal disease except through the possible anabolic effect of certain adrenal steroids released during ACTH therapy. This is considered highly unlikely.

As previously indicated, Blake and others[4] observed no beneficial results from ACTH in the treatment of primary glaucoma. Increased intraocular tension secondary to acute inflammatory disease, however, has responded rapidly to either agent, as mentioned in the reports of Olson and others[13] and Gordon and others.[9] These are both understandable observations and need no further comment. Gordon and others[9] have reported no apparent benefit from ACTH in the treatment of patients with senile cataracts, a result to be expected.

As reported by Woods,[8] topically given cortisone has markedly inhibited the formation of symblepharon in a case of chemical burn; this has been confirmed in the more recent studies of Olson.[22] Thorpe,[26] recognizing the antiphlogistic properties of cortisone and ACTH, has used them effectively in the preoperative and postoperative suppression of inflammation secondary to ocular traumatic injury. One must not hasten to accept the early results as warranting the routine use of these hormones in ocular surgery. Thorn and others[27] believe that there is no clinical evidence that ACTH and cortisone, in the usual therapeutic amounts, will significantly inhibit granulation and mesenchymal healing. In traumatic lesions of the eye, however, the threat of bacterial infection is already great, and in the presence of adrenal hypercorticism or its equivalent in the cortisone-treated patient suppression of tissue response to bacteria may lead to serious infection unless antibiotics are given concurrently.

A further possible limitation of these hormones in ocular surgery is suggested by the studies of Smith and others,[28] in which elevations in the level of circulating heparin or heparin-like material have been demonstrated in a number of patients receiving ACTH or cortisone. That this can alter the dynamics of blood coagulation to the extent of producing hemorrhage in surgical wounds has not been established. Spontaneous bleeding has been seen in a few cases by the authors, yet the evidence of Cosgrift and others[29] suggests that hypercoagulability in some patients also may be observed during therapy with these agents. It is clear from these limited observations that further experimental work is desirable before ophthalmologists can proceed unhesitatingly with the liberal use of either drug in surgery of the eye, in which infection and hemorrhage may prove disastrous.

The recent investigations of Hill and others[30] and Wolfson and others[31] have contributed to a clarification of the functional interrelation of thyroid gland and adrenal cortex. The former workers have demonstrated inhibition of thyroid function by ACTH and cortisone through suppression of thyroid-stimulating hormone output. If, as some believe, thyrotropic exophthalmos is a distinct entity, one might reasonably expect some regression of the exophthalmos in a patient so afflicted and receiving sustained ACTH or cortisone therapy. Convincing evidence of this, however, is lacking. Hill and others[30] adequately treated 4 patients with ACTH and reported that although subjective and objective improvement of congestion was observed the gains were not associated with any significant reduction in the degree of exophthalmos. Failure of ACTH to improve exophthalmos has also been reported by Scheie and others[14] and Olson and others,[13] although in the latter instance the case was considered to be not of thyrotropic origin.

A number of additional but less commonly encountered eye problems have been reported, such as Harada's disease, Vogt–Koyanagi's disease, Coats's disease, Eales's disease and the ocular manifesta-

tions of Tay–Sachs' and Still's diseases. The number of patients with these rare lesions, however, is too limited to justify their inclusion in this review.

Finally, it is not inappropriate at this time to record briefly our unpublished observations on the experimental use of Compound F (17-hydroxycorticosterone)* in the treatment of ocular inflammatory lesions. This compound, whose properties simulate closely those of Compound E (11-dehydro- , 17-hydroxycorticosterone or cortisone) is believed by several investigators[32, 33] to be the most physiologically significant adrenal corticosteroid. To date, we have studied its therapeutic value only as applied topically in 15 patients with acute inflammatory lesions of the anterior segment of the eye. The following have been included: iritis, phlyctenular keratoconjunctivitis, marginal ulcer, the bulbar form of vernal conjunctivitis and congenital syphilitic keratitis. In all cases the rapidity and completeness of therapeutic action have equaled, if not surpassed, that of similarly employed cortisone. The results certainly warrant further study and suggest that Compound F has a high potential therapeutic value, at least in the ocular inflammatory diseases mentioned above.

*Made available for these studies through the courtesy of Merck and Company, Rahway, New Jersey.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 37511

PRESENTATION OF CASE

First admission. A twelve-year-old Negro was admitted to the hospital because of shortness of breath.

It was impossible to secure a complete history of the patient's illness. The parents had been divorced for many years and the patient, an only child, had lived with his grandparents in Georgia until nine months before admission, when he came to Massachusetts to live with his mother and stepfather. He had been a full-term baby, had no known neonatal disease and had apparently developed normally. Two years before entry he developed shortness of breath, apparently associated with diminished appetite, failure to gain weight, weakness and tiredness. Cyanosis of the lips following exertion, associated with breathlessness, also had been noted during this time. About three months and one year after the symptoms first appeared he was acutely ill with an attack of extreme dyspnea. Between attacks the patient lived a very restricted life because of shortness of breath. Since coming to Massachusetts the symptoms had persisted, and he was unable to ascend one flight of stairs without stopping because of dyspnea. He spent one or two days each week in bed and found attendance at school extremely exhausting. He often had to rest before he could eat, his appetite remained poor and he had not gained weight. He slept on two to three pillows and had recently been particularly bothered by dyspnea at night. The patient was said to have had about one episode of slight epistaxis a week during the two-year period and had three-times nocturia more recently. Six weeks prior to admission he experienced acute severe shortness of breath and had a nonproductive cough and some fever. A physician made a diagnosis of "pneumonia," and the patient was admitted to another hospital, where he remained for one month, finally being discharged with the diagnoses of rheumatic fever, rheumatic heart disease, mild cardiac decompensation and bilateral lobar pneumonia. Following discharge he remained in bed most of the time and felt fairly well until one week before entry, when he developed a temperature of 101°F., sore throat and greatly increased shortness of breath. He had had measles some years before entry but no other childhood diseases, so far as was known. Five months before entry an ophthalmologist prescribed glasses for nearsightedness, after which vision improved. Bowel movements occurred two to three times a day and were without gross evidence of blood. There was no history of asthma or other allergy, hematuria, flank pain, joint pains or leg ulcers, and the rest of the systemic review was negative.

There was no family history of heart disease, rheumatic fever, sickle-cell disease, tuberculosis or diabetes.

Physical examination disclosed an acutely ill, undernourished boy in obvious respiratory distress. Respirations were 60 per minute and slightly labored, with no retraction or wheeze. There was an infrequent light cough. The lips, fingers and toes were cyanotic, and there was clubbing of the fingers. The skin was warm and dry. The legs were very thin, with prominent knee and ankle joints. The neck was supple and the ears were normal. Examination of the eyes showed intact extraocular movements, cyanotic conjunctivas and normal scleras. The right pupil was round and reacted to light and on accommodation. The left was smaller than the right and slightly irregular and failed to react to light or on accommodation. The right eyegrounds could not be examined. The retina of the left eye was blanched, but the arterioles seemed normal and without spasm. The disk was irregular and pink, with no edema. There was slight injection of the pharyngeal pillars; the tongue was not red or smooth. The nose was negative except for a small amount of dried blood. The neck veins were pulsating and the trachea was displaced to the right. The heart rate was 156, with the point of maximum impulse in the third intercostal space inside the midclavicular line on the right. There was a gallop rhythm without murmur or thrill. Fine dry crackles were heard over the entire chest bilaterally, with decreased breath sounds at the bases and especially on the right from the apex to the axilla. There was dullness over both bases and dullness to flatness over the right apex to the axilla. Expansion was equal bilaterally. There was a right-sided scoliosis, greatest in the lower dorsal area. The abdomen was soft, flat and nontender, with normal peristalsis. The liver edge was three fingerbreadths below the costal margin and was nontender. Some observers thought the spleen was enlarged. Neurologic examination was negative. There was no peripheral edema.

The temperature was 104°F. and the blood pressure 98 systolic, 65 diastolic.

The urine had a specific gravity of 1.015 and was negative for albumin and sugar. The sediment contained 1 to 2 white cells and occasional red cells and granular casts per high-power field. Examination of the blood disclosed a hemoglobin of 11.5 gm. per 100 cc. The red-cell count was 4,600,000 and the white-cell count 10,700, with 63 per cent neutrophils, 36 per cent lymphocytes and 1 per cent monocytes. The nonprotein nitrogen was 24 mg. per 100 cc. and the blood Hinton test was negative. The sedimentation rate was 48 mm. per hour. A culture of the throat was later reported to have grown abundant alpha-hemolytic streptococcus and a few *Staphylococcus aureus*. Emergency roentgenograms of the chest and abdomen showed a markedly elevated diaphragm. There was strand-like density at both lung bases. The heart was almost entirely contained within the right chest; its configuration and size could not be well outlined because of the elevated diaphragm. The aortic knob was observed on the left. There was increased density in the abdomen and an apparent increase in the anteroposterior diameter. The individual abdominal viscera could not be made out except for a questionably enlarged spleen and liver. An electrocardiogram showed a sinus tachycardia and electrical alternans but was otherwise negative.

During the first sixteen hours in the hospital the patient improved considerably on therapy consisting of oxygen, penicillin and Cedilanid. The temperature fell to 98.0°F., the pulse to 95 and the respirations to 30. An ophthalmologic examination revealed in the right eye small, old corneal opacities near the limbus at three and nine o'clock. The anterior chamber was deep, with a + flare and ++ cells. The pupil was tightly and densely bound to the lens above, below and medially with only a temporal crescent free. In the left eye the cornea was clear. The anterior chamber showed a ++ flare and ++ cells. The pupil was widely dilated and attached to the lens only by a medial strand. Both eyes were negative for keratin precipitates, vitreous opacities or fundal pathology. Tension was normal to the fingers and confrontation fields were full. Skin tests with Old Tuberculin 1:10,000, 1:1000 and 1:100, histoplasmin 1:10 and brucellin were negative. A sickle-cell preparation was negative in twenty-four and forty-eight hours. Urine findings were similar to those on admission except that several specimens gave a + test for albumin. By the second hospital day the white-cell count had fallen to 6700 and by the eighth day to 4800, with a normal differential. The calcium was 8.8 mg., the phosphorus 3.7 mg., the alkaline phosphatase 6.9 units, the total protein 8.38 gm., the albumin 4.11 gm., the globulin 4.27 gm. and the van den Bergh reaction 0.3 mg. direct and 0.5 mg. total per 100 cc. The prothrombin time was 14 seconds (normal, 17 seconds), the cephalin flocculation++ in twenty-four and forty-eight hours, the thymol turbidity 19.0 units per 100 cc. and the thymol flocculation +++. A bromsulfalein test showed 36 per cent retention and a Congo red test 53 per cent retention in the serum. A sputum examination was negative for tubercle bacilli. Fluoroscopic examination of the chest on the sixth hospital day disclosed, in addition to the previous x-ray findings, a normal esophagus. In the right oblique projection, the right heart margin was observed to overshadow the esophagus in a manner characteristic of right-auricular enlargement. The stomach was observed to be beneath the diaphragm and was displaced to the left by an enlarged liver. Slight clearing of changes in the lower lobes noted in the initial examination had taken place. An x-ray film of the hands and wrists showed slight questionable osteoporosis. A second electrocardiogram was within normal limits and a single vital-capacity test measured only 600 cc. A blood culture and a bone-marrow biopsy were negative. Two stool specimens showed + and ++ guaiac tests but were negative for ova.

The patient remained in the hospital sixty-nine days, during which time the temperature, pulse and respiration curves were extremely irregular. The temperature ranged from 98 to 101°F., the pulse from 80 to 150 with an average of about 120 and the respirations from 20 to 60 with an average of about 40. The urine showed little change and the blood hemoglobin remained in the neighborhood of 11.5 gm. Eight white-cell counts ranged from 4400 to 7500, two of which had a normal differential; a third showed 87 per cent neutrophils, 6 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. The red cells were normal. Therapy consisted of 100,000 units of penicillin every four hours for the first nine days, digitoxin 0.1 mg. daily for the first thirteen days and oxygen throughout the hospital stay during periods of shortness of breath. During the last three weeks of admission a nontender swelling over the right parotid area was noted. The gallop rhythm was no longer present.

Final admission (nine days later). In the interval the patient did fairly well for a few days, but the dyspnea returned. The physical and laboratory findings were essentially as before. The right-parotid-gland swelling was still present.

On the fourth hospital day the patient became very dyspneic and a short time later was unresponsive. Respirations were heavy, at 50 to 60 per minute, the pulse barely perceptible and the cardiac rate over 180. The neck veins were very distended. Diffuse moist rales were present over the chest and there was dullness at the right base with diminished breath sounds. The liver edge was 5 fingerbreadths below the costal margin. The patient was areflexic, with unsustained ankle clonus, and there was alternate flaccidity and spasticity of the extremities. The nailbeds were cyanotic; the temperature was

105°F. He was given 0.1 mg. of Cedilanid and oxygen and started on penicillin, following which he improved. An x-ray film of the chest showed no appreciable change and demonstrated basal atelectasis bilaterally (Fig. 1). During the next few days the nonprotein nitrogen rose to a high of 122 mg. per 100 cc. but returned to normal following the administration of intravenous fluids. An examination of the spinal fluid was negative. Over a period of seven days following the acute episode the patient gradually improved and was permitted slight ambulation. At this time laboratory studies disclosed that the total protein was 9.18 gm., the albumin 3.51 gm., the globulin 5.67 gm. and the nonprotein nitrogen 26 mg. per 100 cc. Two days later the right ankle became hot, tender and swollen, and firm nodules were noted in the calves of both legs. During the next twelve days there was progression of the joint symptoms, with involvement of the knees, shoulders, elbows, wrists and fingers. This usually took the form of acute episodes lasting four to five hours, associated with elevation in temperature to about 103°F. but with no change in the white-cell count or differential. Nine days after the onset of joint symptoms, although he had seemed to be improving somewhat, the patient was found in coma. The temperature had fallen to 94°F. and the respirations to 10 to 15 per minute. The pulse was strong and steady, with a rate of 120; the blood pressure was 110 systolic, 60 diastolic. The neck was rigid, and there was a wandering movement of the eyes, with alternating divergent strabismus. The pupils did not react, the extremities were flaccid and there was a tremor of the lips. During the next forty-eight hours the patient lapsed in and out of coma; early on the third day he was found dead.

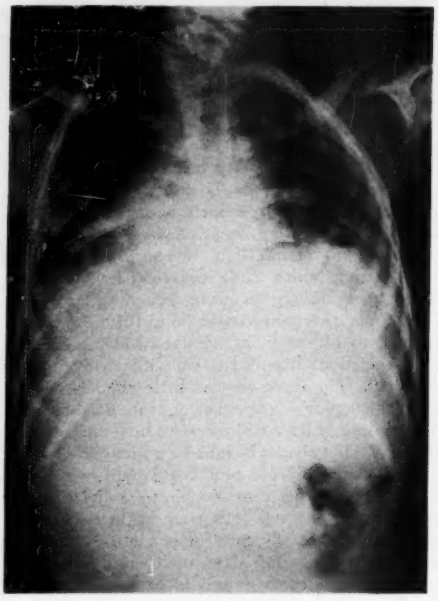

FIGURE 1.

During this final admission therapy had consisted of digitoxin, penicillin, sulfadiazine and intravenous fluids. Numerous urine specimens showed specific gravities ranging from 1.005 to 1.012; nearly all gave + to ++ tests for albumin and contained occasional casts, red cells and white cells in the sediment. The average of some twelve vital-capacity determinations was about 600 cc. Several blood cultures were negative. Terminally the serum chloride was 94 milliequiv. per liter and the nonprotein nitrogen 90 mg. per 100 cc. During the last week of life there was a progressive elevation of the white-cell count to 41,500.

DIFFERENTIAL DIAGNOSIS

DR. SIDNEY FARBER*: May I see the x-ray films at this time?

DR. JOSEPH HANELIN: A great many chest films were taken during the course of the patient's illness. The diaphragm is considerably elevated in all the films, and a streaky and granular density is present in both lungs, largely confined to the lower lung fields, but there is some infiltration present in the remainder of the lungs. As you can see, the heart is very peculiarly placed in the thorax; the bulk of the heart lies within the right chest; the aortic arch and descending portion of the aorta lie on the left side normally. It was thought that rather than representing a congenital abnormality this was the result of an elevated diaphragm with perhaps an enlarged right auricle. The films show various degrees of pulmonary involvement throughout the course of the patient's illness. There is evidence of both hepatic and splenic enlargement. As far as the hands and toes are concerned, there is very little change visible. I am not certain of bone disease; osteoporosis is somewhat questionable.

DR. FARBER: The problem here, then, concerns a boy of twelve years whose illness began in Georgia two years before entry at the age of ten and nine months before he came to Massachusetts. Chiefly there was dyspnea, evidence of cardiac disease and congestive failure. He had enlargement of the liver and spleen, undoubtedly associated with congestive failure, and in addition he had evidence of liver disease and some degree of kidney disease, which might better be explained by some condition other than the congestive failure. He had also involvement of the eyes that was very well described in the protocol. An ophthalmologist whom I con-

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sulted told me that he thought this meant intraocular inflammation, — there was keratitis, iritis and uveitis, — and that picture is well enough known as a part of an inflammatory process. However, it could occur with a number of unrelated conditions not of an infectious nature. A nontender swelling of the parotid gland was noted during the last five days before death. Moreover, standing out very clearly were the hyperproteinemia and the great increase in globulin. These are the points I should discuss before attempting to arrive at a diagnosis.

The congestive failure appeared to be both left and right sided. There was no evidence of dextrocardia in the electrocardiogram, which was normal except for the sinus tachycardia. There were no murmurs or thrills two years after the onset of cardiac failure. Then I may exclude rheumatic heart disease. It would be most unlikely for such a serious rheumatic heart disease to be present for two years without some change in the electrocardiogram or thrills or murmurs. There was no evidence of hypertensive, syphilitic or congenital heart disease. Sickle-cell anemia with cardiac involvement appears to have been excluded.

I shall then consider myocarditis. It is possible to have, with the electrocardiographic changes and the physical signs that have been noted, a myocarditis that points to no one specific cause. There was a response to digitalis and digitalis-like preparations, but I understand that does occur with acute myocarditis, according to Dr. Alexander Nadas, a colleague whom I consulted on this point. The myocarditis may not have been of the usual forms encountered with ordinary infectious agents such as streptococcus and similar organisms. Polyarteritis nodosa with diffuse involvement of small vessels not only in the myocardium but elsewhere may present a picture of this kind. There is an extraordinary disease known as Fiedler's myocarditis, — either the diffuse form or the definite granulomatous or the very isolated form, — that could well account for this picture. Then, too, myocardial and pericardial involvement occurs in the disease known as sarcoidosis.

The cardiac picture may have been produced by obstruction to the function of the heart, to the flow of blood; the myocardial failure may have been due either to a mediastinal mass or to some other lesion, — I am thinking of a diverticulum of the esophagus, which may occur even at this age, — or to malformation of the esophagus; that appears to be excluded. I should think of tumor in the mediastinum, such as a teratoma or a slowly growing thymoma, which may produce this kind of cardiac failure, or of infiltrations of the mediastinum secondary to a chronic leukemia, lymphosarcoma or Hodgkin's disease. And, as I learned to my great edification in this room several years ago, there may be cardiac embarrassment and symptoms of a tumor secondary to the disease coccidioidomycosis. This patient came from Georgia but that disease is not by any means restricted to California. I shall not list the whole series of diseases that may involve the myocardium and the lymph nodes in the mediastinum and that are all related to the general group of infectious disorders of which coccidioidomycosis is but one member. Myocardial involvement may occur in heart failure secondary to lung involvement and there was evidence of lung disease. However, the failure was on both sides and would make me look for something more than just pulmonary involvement to explain the picture. The heart was in the right chest either because there was a mediastinal mass pushing it over or because there were adhesions pulling it over. Could there have been a pericarditis?

Could you exclude a tumor of the mediastinum or a series of masses in the mediastinum by x-ray examination?

Dr. Hanelin: There is no definite indication for a mediastinal mass. The mediastinal configuration can be explained by the placement and contour of the heart.

Dr. Farber: May I summarize the eye signs once more: intraocular inflammation with keratitis and iritis. There was no mention of the use of ACTH (adrenocorticotrophic hormone). Perhaps this patient was in the hospital before the era of ACTH — or I am sure it would have been tried; that might have been helpful in a very general way but certainly not in a specific manner. This kind of eye disease, — and I display once more the joy of recently acquired knowledge, — may be associated with tuberculosis, sarcoidosis, syphilis, brucellosis, rheumatoid arthritis and leukemia. There was no evidence for any one of these on examination of the eyes alone. The parotid swelling, which was nontender and was present for only five weeks, is extremely interesting. Involvement of the uveal tract and the parotid gland, called uveoparotid fever of Heerfordt,[1] may be associated with sarcoidosis, tuberculosis, leukemia and lymphoma.

The hyperproteinemia plus the great increase in the globulin level is perhaps the most important single laboratory finding that was mentioned. This combination is found in conditions as unrelated as multiple myeloma, pneumonia, subacute bacterial endocarditis and rheumatic fever and occasionally in osteomyelitis, pulmonary abscesses, lymphogranuloma venereum and sarcoidosis. There are other conditions responsible for an increase in globulin alone, but I shall not consider them, as both the total protein and the globulin level were elevated.

What are the possibilities in explaining this very long story? The disease picture is not completely characteristic of any one that I can think of. Could this have been leukemia, lymphoma or thymoma? I think those possibilities do exist. There was no

evidence of the presence of a tumor in the x-ray films and no evidence from the bone-marrow examination of a lymphomatous process. The destruction by tumor, — any kind of tumor, — for a long period of time may have been responsible for the marked elevation in the protein and globulin, and the eye signs and cardiac signs could conceivably be so explained. The changes in the kidneys may also have been a part of a widespread tumor process.

Could this have been a combination of two separate unrelated diseases, a tumor in the mediastinal area, which I cannot quite leave from the discussion, and tuberculosis or some other infiltrative or inflammatory process of the eye? I think that possibility must be mentioned. However, I shall continue to explore to find one disease that will explain everything, unless that is impossible.

I mentioned polyarteritis before. Patients with polyarteritis frequently die in acute congestive failure. Although it is a very rare disease in children, it does occur at this age. Lacking any other evidence of arterial or vascular involvement, I am afraid, I can do no more than mention the possibility.

There are two other possibilities that I shall consider briefly. The first of these is rheumatoid arthritis, but there were many things lacking for a typical story of rheumatoid arthritis. I am very much interested in the involvement of the joints with nodules during the last two weeks of the final admission. The rest of the story is not typical of rheumatoid arthritis. The second of these is a condition that I have called, for lack of a better name, lipogranulomatosis. Dr. Ropes will remember a much younger patient whom we saw together some years ago whose history of heart involvement, clarified at autopsy as both pericardial and myocardial, and involvement of the joints by nodules reminds me very much of this. The difference between the two patients is one of duration of illness and of the sequence of events. That disease (lipogranulomatosis), which histologically resembles Pick–Niemann's disease and in its granulomatous nature resembles Schüller–Christian disease and yet is neither one of these, may give a picture in many ways similar to the one under discussion. Although I have no evidence that would permit me to make that diagnosis, I think I am justified in thinking of it.

Finally, what does all the evidence point to more than to any other condition? In the condition known as sarcoidosis, which most of us do not believe is a form of tuberculosis, there may be myocardial and pericardial involvement. It is nonspecific in distribution and in character in that many other conditions may produce the same kind of gross or clinical picture, but nevertheless the myocardium and pericardium may be involved. Longcope and Fisher[2] in 1942 described six patients with cardiac lesions involving the pericardium and myocardium who had sarcoidosis; in those who came to autopsy the diagnosis was verified microscopically. In sarcoidosis, too, there may be mediastinal lymph-node involvement with obstruction to the vascular system. There was a great deal of cardiac failure here, and possibly some of it was produced by enlargement of the lymph nodes somewhere along the great vessels. Strand-like density in both lung fields over both lung bases is a finding that is perfectly consistent with a pulmonary involvement, which is more familiar to all of us as a part of sarcoidosis. There was a right scoliosis, greatest in the lower dorsal area, but whether or not it was based on any bone destruction I do not know. Osteoporosis of the terminal phalanges if present was not very striking. In sarcoidosis, the terminal phalanges of the hands and toes particularly are involved in an osteoporotic process sometimes so severe as to be very readily recognized. Keratitis and uveoparotitis are all part of a sarcoid process, so that would fit very well, as would the involvement of the liver and the kidneys. The monocyte count may be increased for a long period of time, and terminally the central-nervous-system picture may have been produced as part of a sarcoid involvement or simply as a result of pulmonary edema with sinus thrombosis in a dehydrated child. Finally, the high protein and high globulin are quite characteristic of sarcoidosis. By exclusion and by a process of reasoning I have reached the conclusion that sarcoidosis is probably the proper diagnosis. I have no evidence that would make the diagnosis, and the only evidence possible would be actual histologic study of a removed lymph node or of a subcutaneous nodule.

Dr. Edward F. Bland: May I ask a question? I am not clear as to what Dr. Hanelin thinks about the shape and position of the heart.

Dr. Hanelin: We were quite troubled by that ourselves when we first saw the films. The first thing that occurred to us was the question of a congenital cardiac abnormality of some type; it was thought that dextrocardia might perhaps be ruled out, as the aorta lay properly and there was no inversion of abdominal viscera. On fluoroscopy it appeared that the right lower-mediastinal prominence represented a portion of the heart, and with the presence of cardiac failure it was regarded as the right auricle.

Dr. Bland: The shape of the heart in the face of an entirely normal electrocardiogram bothers me. We have had three patients with a cardiac silhouette of this shape, two of whom have been catheterized; we think that they are normal hearts abnormally rotated, for which we have no explanation.

Dr. Hanelin: There is a scoliosis of the upper third of the thoracic spine, secondary to a congenital abnormality, hemivertebra.

Dr. Bland: The silhouette does not look like that of a failing heart due to myocarditis.

DR. FARBER: The hemivertebra in that area is frequently associated with an abnormality of the trachea and esophagus (tracheoesophageal fistula). Could there be a remnant of a strand representing an old tracheoesophageal fistula or one that has become a tracheoesophageal fistula?

DR. MARIAN W. ROPES: We thought that sarcoidosis would explain almost everything. We were a little disturbed by the joint involvement. Joint involvement can occur occasionally in sarcoidosis, but it is not common. We believed that acute attacks of this type with definite objective findings were unusual. We thought, as did Dr. Farber, that the other involvement, particularly of the lungs and the liver, was greater than that seen in so-called generalized connective-tissue disease.

DR. BLAND: Another thing, Dr. Farber: I am bothered by the degree of circulatory involvement two years before the patient actually died, if it was due to sarcoid infiltration of the heart.

DR. FARBER: It does seem to be extraordinarily long, and I should be very much happier if there had been something to suggest large lymph nodes or masses. I should like to place the lesion outside the heart rather than in it.

DR. HANELIN: Could this not be explained by chronic involvement of the lung parenchyma?

DR. BLAND: When the heart once fails from pulmonary disease, it does not usually recover very well. The patient does not live two years with relatively good health between attacks.

DR. JOHN T. QUINBY: Is any light thrown on the situation from the cases reported by Dr. Earle Chapman[3] years ago? He described adults with considerable structural scoliosis; some of them died in congestive failure.

DR. BLAND: I do not think we could fit that in. Usually there is some evidence in the electrocardiogram of right-ventricular preponderance and strain.

CLINICAL DIAGNOSES

Pulmonary congestion.
Cardiac weakness from myocarditis.
?Sarcoidosis.

DR. FARBER'S DIAGNOSIS

Sarcoidosis.

ANATOMICAL DIAGNOSIS

Wegener's granulomatosis.
?Sarcoidosis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: During the first admission an aspiration liver biopsy was done and we did find a few small granulomas with foci of necrosis. They were epithelioid in character but did not look like the clear-cut sarcoid tubercles, which are not supposed to have central necrosis. For want of a better diagnosis we called it sarcoidosis on the biopsy, but we were not happy about it.

At autopsy the heart weighed 220 gm., which is almost twice normal for a child of this age; the liver and spleen were enlarged, weighing 1200 gm. and 350 gm. respectively. The lungs were not very abnormal grossly — moderately congested. We were unable to feel any definite nodules, which are often present in sarcoidosis. The lymph nodes were not large. Those around the hilus of the lung were slightly enlarged but did not look too abnormal. They were not the large nodes characteristically associated with sarcoidosis. We could not make any diagnosis in the gross except enlargement of the heart, liver and spleen.

DR. BLAND: Could you tell us a little more about the size and position of the heart?

DR. CASTLEMAN: The auricle was big and pushed over to the right, possibly by the enlarged liver.

DR. BLAND: It was an enlarged heart in an unusual position.

DR. CASTLEMAN: The microscopical sections are very puzzling. This slide of the lung shows a granulomatous lesion near the pleural surface that looks like a sarcoid nodule (Fig. 2). Note the giant cells; there were nodules similar to this in other parts of the lung. In other fields were abscesses with many polymorphonuclear cells, and many of these abscesses surrounded blood vessels. In the next slide are a small artery with periarterial infiltration and necrosis of the arterial wall and another one with fibrinoid necrosis of the wall of the vessel with inflammatory reaction around it (Fig. 3). There were numerous areas with both types of lesions throughout the kidneys; in addition, in some of the tubules we found casts that could be sulfonamide crystals. The combination of granulomas and what looked like polyarteritic lesions has been described by Wegener.[4,5] Similar lesions were found in the heart, liver, spleen, brain, parotid gland and uvea. Dr.

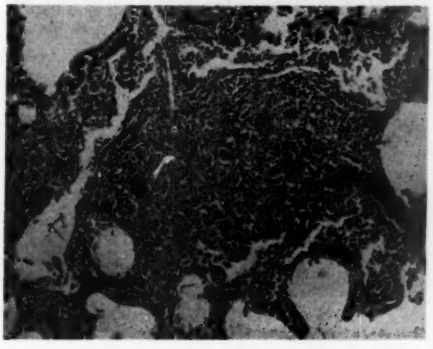

FIGURE 2.

Parker Heath examined the eyes and made a diagnosis of vasculitis and granulomatosis. We have, then, that syndrome that is called Wegener's granuloma, or granuloma associated with polyarteritis. It has been thought that most of the cases of Wegener's granuloma have been associated with hypersensitivity. Whether the patient had received sulfonamides in Georgia or not and whether that may have started this I do not know. The other possibility is that the patient had an underlying sarcoidosis and that the final illness was the result of a hypersensitivity, which led to the development of the arterial lesions. We have had 2 other cases on which Dr. Mallory has made a diagnosis of Wegener's granuloma — and the slides were not unlike many of these.[6]

Would you like to comment, Dr. Farber?

Dr. Farber: I should like to suggest that the term "sarcoidosis," which we all recognize as a

Figure 3.

nonspecific term, might still be the best one here. We had a case of unquestionable sarcoid disease in a child whose first bowel lesion appeared fourteen years before the occurrence of a necrotic process in the skin and subcutaneous tissue. The child had never received sulfonamides; this was in the era before the antibiotics could disturb research as much as they now do. I think there is very little to be gained by using this term as an indicator of a new disease. I think the evidence for implicating the sulfonamides has been rather questionable. I should like to leave it as a granuloma of unknown etiology with subacute or necrotic portions, as part of the picture as they are in a great number of infectious granulomas.

Dr. Bland: Would you accept the earlier heart failure as a result of an acute reaction in the myocardium that may later have healed and permitted the patient to improve?

Dr. Castleman: The heart showed many of the granulomas, as well as a diffuse myocarditis. Perhaps the sarcoidosis antedated the arteritis.

Dr. Jacob Lerman: Were there no large lymph nodes in the mediastinum?

Dr. Castleman: Not very large. There were some slightly enlarged lymph nodes but not enough to produce pressure. They showed a healed granulomatous reaction. I think we shall have to call it a granuloma without any question, but it does not fit the usual case of sarcoidosis that we have seen; most of the joint symptoms that this patient had do not usually occur with sarcoidosis. I think we have to assume that he had some hypersensitive reaction with or without an underlying sarcoidosis.

Dr. Ropes: There have been other cases of connective-tissue disease, such as dermatomyositis, in which the lesions were indistinguishable pathologically from ordinary sarcoid as found in many of the lymph nodes in the abdomen.

Addendum

Dr. Castleman: After the conference the microscopical slides and the discussion were submitted to Dr. David Freiman,[7] who has studied all our sarcoid material, for his comment.

Dr. David Freiman: There are many clinical features in this case that are often associated with sarcoidosis, as Dr. Farber has pointed out, and the granulomatous lesions, — at least those seen in the lung, — are also consistent with such a diagnosis. There are many other features, however, that are in no way characteristic of this disease. The severe dyspnea and cardiac involvement that this patient presented is not seen in sarcoidosis in the absence of severe pulmonary fibrosis and secondary cor pulmonale, and autopsy examination failed to reveal these complications. Nor are the joint symptoms here described a manifestation of this disease, the joints rarely being affected — and never in this acute fashion. If this patient had sarcoidosis, therefore, it has clearly been complicated by another widespread process. The disseminated necrotizing angiitis described is of the type that Zeek and her co-workers[8] have labeled "hypersensitivity angiitis" — an intense reaction of relatively short duration, usually seen in lung vessels as well as elsewhere. This process is clearly of recent origin. It probably accounts for the patient's terminal illness and marked joint reaction, and it is possible that the diffuse interstitial inflammation seen in most of the tissues examined is part and parcel of this process. On the other hand, in view of the prolonged history of dyspnea and cardiac insufficiency, the process may have been more fundamental. The granulomas present in the lung and elsewhere may under these circumstances be related to this latter process, and there are areas in the lung and lymph nodes where the two processes seem closely linked. Similar changes have been seen in the lungs and livers

of patients dying with prolonged chronic beryllium intoxication, in which an intense chronic interstitial inflammation is associated with granuloma formation and in which severe dyspnea is a prominent symptom. A number of agents appear capable of inducing such a reaction, and it is well known that the sarcoid lesion is in no way specific for the disease sarcoidosis. I would be inclined, therefore, to assume that this patient had an underlying disseminated disease of unknown etiology associated with interstitial inflammation and granuloma formation, complicated terminally by a disseminated necrotizing angiitis and exaggeration of the interstitial inflammatory reaction.

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CASE 37512

Presentation of Case

A thirteen-year-old girl was admitted to the hospital because of pain in the right shoulder.

One year before admission she first noted a dull aching pain in the right shoulder joint, usually precipitated by overexertion. The pain would disappear spontaneously after a variable length of time. The episodes gradually increased in frequency and severity and finally occurred occasionally without exercise. When the arm was at rest, on some occasions the pain was severe enough to keep her awake at night. There was a gradual loss of strength in the right arm, and although normally right handed she did most things with her left hand because she was afraid that movement of the right arm might precipitate the pain. There was no swelling or tenderness of this joint and there was no other joint or bone tenderness, swelling or pain.

Three years prior to admission she fell from a tree and sustained a few superficial injuries — short-lasting bruises of the right axilla and abrasions of the skin of the left shin, which later became superficially infected. She had had measles, chicken-pox and mumps but no serious illnesses. There was no significant familial history.

A few months before admission she was referred to the Neurological Out-Patient Clinic. Examination there revealed some weakness in the right arm and moderate atrophy of the muscles of the right shoulder, but no evidence of neurologic disease was found. A roentgenogram of the right shoulder showed a localized cyst-like lesion measuring 2 by 1.5 cm. in the head of the humerus (Fig. 1). This did not extend to the cortex except in one position, in which it approached the joint surface. The base of the lesion extended to the epiphyseal line. A slight margin of increased density surrounded a part of the lesion. X-ray films of the left shoulder and cervical vertebras were negative.

Figure 1.

Physical examination revealed a well developed, well nourished girl. There was mild tenderness on deep pressure of the anterior aspect of the right humeral neck. The right shoulder joint had a full range of painless motion, both active and passive, without spasm, except that there was some slight limitation of active hyperextension. No swelling or bony abnormality in relation to this joint was noted. All other bones and joints were normal. There was a slight decrease in muscle strength in and moderate atrophy of the right biceps, triceps and deltoid. The remainder of the physical examination was noncontributory.

The urine was normal. Examination of the blood showed a hemoglobin of 13.4 gm., a sedimentation rate of 16 mm. per hour and a white-cell count of 6200, with a normal differential. The calcium was

9.7 mg., the phosphorus 5.3 mg. and the alkaline phosphatase 6.7 units per 100 cc. A tuberculin skin test, 1:10,000, was negative. An x-ray film of the right shoulder showed the lesion previously described to have increased slightly in size. X-ray films of the pelvis, hips, spine and chest were negative.

On the fifth day an operation was performed.

Differential Diagnosis

Dr. Joseph Hanelin*: Let us first look at the lesion as demonstrated in this film (Fig. 1). There is a 2-cm. slightly lobulated ovoid radiolucent zone within the medial aspect of the right capital humeral epiphysis. It is sharply demarcated and is partially bounded by a thin sclerotic line. It extends to the articular cortex superiorly, and its lower margin rests at the epiphyseal plate. It does not extend into the diaphysis. There is slight overgrowth of the humeral head medially so that it overhangs the shaft more prominently than on the normal left side. This is a nonspecific response and could result from almost any lesion — vascular, infectious or neoplastic. Moderate bone atrophy is present about the right shoulder. This is the lesion as it appeared just prior to surgery; in comparison with a film taken three months before it had increased slightly in size. A complete skeletal survey and chest films disclose no other abnormality.

From the history it is evident that the lesion had been present for at least one year. The patient's general health was good, and the physical examination disclosed only those changes that might accompany any painful lesion near a joint. There was no clinical evidence of joint disease, nor is there any indication of joint involvement by x-ray examination. The laboratory studies were all within normal limits, and a generalized metabolic bone disorder such as hyperparathyroidism can be immediately dismissed.

The history of an injury three years previously warrants some comment, albeit brief. Trauma has, of course, been assigned by various authorities as etiologic for a variety of bone lesions, — neoplasms, cysts and granulomatoses, — but real proof for this is lacking. I doubt that even after the histology is made known to us it will be possible to indicate trauma as the causative agent. The superficial infection of the skin would not appear important, particularly with the two-year time lag before the onset of complaints.

Of considerable help is the location of the lesion — totally within the cancellous portion of the epiphysis of a growing child. Review of the literature and our own teaching file shows that only a relatively small number of lesions occur in this portion of the extremity and that it is a site of predilection for only one rather rare benign bone neoplasm. This may be related to the much greater and more rapid growth of the diaphysis than of the epiphysis. Morphologically the cyst-like defect is not distinctive, and this hole in the bone could be filled by fluid, an abscess, a granuloma or a benign neoplasm. This was a slowly-developing process that had endured over a year, and I believe that malignancy, either primary or metastatic, could be ruled out almost on this basis alone; in addition, there is no clear-cut x-ray evidence of a malignant process.

I shall attempt to exclude, if possible, infectious lesions of specific etiology. Bone tuberculosis comes first to mind. It may cause a cyst-like defect within the cancellous portion of the bone; the history of gradual increase in pain is in keeping with this possibility. It is not likely, however, to respect either the epiphyseal plate or the articular cortex — as is true in this case. A greater degree of bone atrophy might be expected, as well as more rapid bone destruction. The presence of a negative tuberculin skin test and absence of any systemic manifestation virtually eliminate bone tuberculosis.

In tertiary syphilis a greater degree of sclerosis surrounds the zone of bone destruction, and there was no clinical indication of syphilis. Various other specific infections might also be mentioned, although there is no real proof of their presence.

Mycotic infections would be expected to advance more rapidly, extend into the joint and cause systemic manifestations.

Brodie's abscess, which is a localized, chronic zone of osteomyelitis generally due to *Staphylococcus aureus*, is less easily disposed of. It must be regarded as a distinct possibility from both the clinical and roentgenographic viewpoints. Generally, however, it involves the metaphyseal portion of the diaphysis and may be expected to show a greater degree of surrounding sclerotic reaction. It tends to be restricted by the epiphyseal plate, although occasionally it will cross it.

Of the granulomas of unknown origin, eosinophilic granuloma must be mentioned as a real possibility. Eosinophilic granuloma most commonly exists as a solitary lesion. It causes a localized zone of bone destruction without appreciable sclerotic reaction, although in the shafts of long bones it may stimulate periosteal new-bone formation. It is frequently accompanied by some leukocytosis and mild eosinophilia. The type of pain felt by this patient is not uncommon.

In the category of benign bone tumors a rather large number of possibilities present themselves, a number of which might be summarily dismissed. The solitary unicameral bone cyst appears in this age group but is generally accompanied by little or no pain until a pathologic fracture occurs. It is always found in the diaphysis, never in the epiphysis.

Osteoid-osteoma, regarded as a benign neoplasm by Jaffe and Lichtenstein[1] and as response to infection by others, will cause pain such as this patient

*Associate radiologist, Massachusetts General Hospital.

experienced. The roentgenographic features, — absent in this case, — are fairly distinctive and consist of a small central radiolucent nidus surrounded by a huge dense reactive zone.

Giant-cell tumor appears improbable. These tumors almost always occur after epiphyseal closure and are extremely rare under the age of twenty — so much so that much doubt is cast on such a histologic diagnosis of a lesion found in the actively growing period. This tumor generally arises in the epiphysis and secondarily extends into the shaft. Giant-cell tumors are usually larger in size than in this case — particularly with symptoms of this duration.

Nonosteogenic fibromas of bone and fibrous dysplasia are unlikely, largely on the basis of location. These lesions are almost invariably located in the diaphysis. Even with widespread polyostotic fibrous dysplasia epiphyseal changes are rarely seen, and I personally am not familiar with localized fibrous dysplasia that has only affected an epiphysis.

Central chondroma is a lesion that I cannot definitely rule out; it is extremely rare, however, in long bones and is most commonly present (over fifty per cent of cases) in the bones of the hands or feet.

Chondromyxoid fibroma of bone, recently described by Jaffe and Lichtenstein[2] and often mistaken for chondrosarcoma, also occurs in the diaphysis; in this condition the bone is considerably more expanded than it is in the case under discussion.

A benign chondroblastoma of the bone, so named by Jaffe,[3] although originally described in 1928 by Ewing[4] as a calcified giant-cell tumor and more extensively elaborated on by Codman[5] as an epiphyseal chondromatous giant-cell tumor and regarded by him as a giant-cell variant, appears to be the most likely probability. This lytic lesion may show varying amounts of calcification and is slowly growing. It is benign and responds to simple curettement. The age incidence and the history of pain in this case are in keeping with such a lesion. These generally average about 3 cm. in size, and only in a few cases have they been reported as larger than 6 cm.

These lesions are most commonly found in males. In all cases in the literature these have invariably been reported as originating within the epiphysis and as generally remaining confined to this portion of the bone. Where the diaphysis is involved, it appears in all cases to have been secondary to extension of the lesion from the epiphysis. In Codman's group of 9 cases the lesions were present only in the shoulder — probably because the shoulder was of particular interest to him. However, in the other 16 cases found in the literature, although the epiphyses were affected the shoulder did not preponderate as the site of predilection. Histologically, this lesion is believed to have taken origin from cartilaginous germ cells. The giant cells present are osteoclasts found in areas of necrosis, hemorrhage or chondroid organization.

In conclusion, I regard this process as a localized solitary benign lesion; I am not absolutely certain of the histology, although I favor chondroblastoma as most likely on the basis of site, age incidence and slow growth. An eosinophilic granuloma cannot be ruled out; a more remote possibility is a Brodie abscess.

Clinical Diagnosis

?Chondroma of humerus.

Dr. Hanelin's Diagnosis

Benign chondroblastoma.

Anatomical Diagnosis

Benign chondroblastoma of right humerus.

Pathological Discussion

Dr. Benjamin Castleman: This patient was operated on by Dr. Edwin Cave, who on exposing the joint found definite thickening of the synovial capsule. An opening was made at the junction of the articular cartilage and the epiphyseal plate; the drill was aimed upward toward the inner aspect of the humeral head and led into a cavity that was filled with grayish-pink soft material containing many yellowish flecks. All of it was curetted. The cavity was left open and the wound closed.

Microscopically we were able to confirm Dr. Hanelin's diagnosis of benign chondroblastoma. In addition to the characteristic large cells with, as Jaffe has so aptly described it, an aura of cartilage, there were the pathognomonic large foci of necrosis and calcification. As Dr. Hanelin has stated, this is a rare tumor but one that should not be overdiagnosed as a giant-cell tumor or a chondrosarcoma.

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The New England
Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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JINGLE BELLS

IT HAS been an old custom with the *Journal* at this season to prepare and release some sort of editorial statement concerning Christmas. This has usually been in the nature of a brief comment on the advantages of good will among men and the desirability of peace on earth. Depending partly on the world conditions that happened to prevail at the moment and partly on the state of mind of the particular editor who was responsible for the release, the tone of the editorial has been *a:* hopeful or *b:* unhopeful. There is no indication that these efforts, regardless of their literary merit, have as yet made any impression on the global situation.

This year the editors have decided to withhold their annual attempt to promote the good-will industry and to give a try, instead, to the equally prevalent custom of presenting their own Christmas list and to see what comes of it.

Here is what the editors would like for Christmas — and, indeed, for the whole new year.

They would like to receive a reasonable number of top-flight new manuscripts, — perhaps 250, — from which they could make their choice, containing from 800 to 4000 words each, recently typed with double or triple spacing (including the case reports, footnotes and references) with a reasonably fresh ribbon. They would like to have the references limited to those of real significance, following accurately the style of the *Cumulative Quarterly Index Medicus*. (The only impression that inflated "bibliographies" make is a bad one.)

Needless to say, — perhaps, — any paper that is fit to be published is written in as good English as the author can muster and is then rewritten at least twice, with a number of words discarded at each writing; for anything that is worth saying at all is usually said twice as well in half the number of words. Its tables and charts are few and simple, and properly captioned. In its final state it is crystal clear and informative and meets some need other than that of the author for publicity.

After all, the only really valid reason for writing a scientific medical article is to present the results of useful investigation or seasoned experience, thus adding to the sum of medical knowledge, or to bring together and correlate existing knowledge in order to make it more easily available. Only occasionally is a single case worth reporting, to remind a journal's readers of the existence of some condition that may cause diagnostic confusion or to add to the knowledge of its treatment; it should be reported with the utmost brevity. A case report should always point a moral, whether or not it may adorn a tale.

The editors would like to find in their stockings the promise of a series of inspired and carefully worded editorials on a variety of pertinent subjects, and a salty but amiable correspondence suitable for publication. They would be pleased with a strict observance of deadlines on all promised material.

Given these things, a circulation that continues to expand, and a growing list of contented advertisers, they will believe that there really is a Santa Claus!

ANTIBIOTIC COMBINATIONS

Evidence is accumulating that one cannot glibly assume, as is commonly done by many practitioners, that if one antimicrobial agent is useful in the treatment of an infection, two or more similar agents having the same or comparable activity must be even more beneficial. It was natural that after the introduction of penicillin many physicians still thought it necessary to prescribe the sulfonamide drugs in combination with that antibiotic. They had previously seen startling results from the sulfonamides, and they now also wished to give their patients the benefit of the new "magic weapon." In spite of numerous indications that little if any benefit is gained by adding the sulfonamides to penicillin for the treatment of those infections against which penicillin is highly active, this combination is still commonly used and several manufacturers are now incorporating triple sulfonamides with penicillin.

The pharmaceutical manufacturers are not entirely to blame, for they will concoct any combination of agents that the medical public demands or can be persuaded to buy — and that will pass the relatively minor requirements of the licensing authorities. In this instance the incorporation of four agents obviously increases the chances of sensitization and other toxic effects at least fourfold and leaves the physician in the dark, when evidence of toxicity occurs, about which one or more of the components is responsible. Furthermore, most of the conditions for which they are recommended will probably respond to one or another of the components separately or else will not respond to all of them in combination.

Evidence at hand indicates that certain combinations of antibiotic agents may be useful whereas other combinations may actually be antagonistic. This evidence stems largely from laboratory studies, but is nevertheless impressive. Spicer[1] studied the in-vitro effect of aureomycin, chloramphenicol, streptomycin, dihydrostreptomycin, penicillin and bacitracin on strains of several bacterial species. When these antibiotics were used in pairs, four types of effects were observed, depending on the particular combination of drugs for a given bacterial strain. Some pairs of antibiotics appeared to act synergistically; the action of other combinations seemed to be additive; still other agents seemed to have no appreciable effect on each other, whereas some actually appeared to interfere with the inhibition produced by another active antibiotic. Elsewhere in this issue of the *Journal* a case is presented in which combined therapy with two antibiotics, judiciously applied after proper laboratory control, may have proved lifesaving.

Jawetz and his co-workers[2-4] have shown that both in the test tube and in experimental infections chloramphenicol, aureomycin and terramycin may interfere with the action of penicillin on the growth of enterococci. They have also demonstrated similar interference in the case of other organisms and combinations of antibiotics. They indicate that the type of drug incompatibility that they were able to demonstrate between chloramphenicol and penicillin in vitro and in experimental infections may have to be taken into account in future considerations of multiple antibiotic therapy.

Such antagonisms have not been clearly demonstrated in the treatment of human infections. Nevertheless, in spite of the many reports suggesting that favorable effects may be obtained from the combined use of antimicrobial agents, the wise physician will be on the lookout for possible harm to his patients resulting from the indiscriminate use of multiple agents — particularly when adequate effects can be obtained from the judicious and controlled use of the same agents when they are administered individually.

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DOMUS MEDICA

The truly essential domicile for any association of physicians is in the hearts and minds of its members; more material residences may be desirable as practical conveniences for the carrying on of

business, as repositories of inspirational material arranged in inspirational surroundings, or as places to rest the feet.

The home of the American Medical Association in Chicago is an office building, purely and simply functional; whatever of inspiration and romance may have its origin in the banding together of physicians in a common interest is not here betrayed by any heraldic symbols or by any obvious designs revealing the intent of architects that enduring principles should be housed in abodes of lasting beauty.

The building in Tavistock Square that shelters the British Medical Association typifies the impressive dignity that is characteristic of Great Britain — a steep-roofed mass of brick and stone, enclosing a grassy quadrangle behind iron grilles and containing a high-ceiled convocation hall. The Colleges and the Royal Society of Medicine have also their appropriate strongholds.

The Massachusetts Medical Society may take credit for its own new home, the first that it has ever owned and fully occupied — a dignified former private residence, which has been converted to the practical uses of the Society with the beauty of its original interior retained.

The Danish Medical Association, with a somewhat smaller membership than that of the Massachusetts Medical Society, has also found itself a new and stately home in Copenhagen — its *Domus Medica*. This recent move to a more spacious mansion did not result from any previous long-laid plan but from one of those exigencies occasioned by the "model" occupation with which the friendly Nazis showed their good will to the Danish people during the recent war.

Various elements of the subjugated country seemed not to appreciate at that time the newer culture that was being showered on them; among these recalcitrants appear to have been the majority of the Danish physicians, who earned the ill will of the conquerors. There were, however, collaborators — among them a medical student who was discovered to be plotting the betrayal of one of his professors.

When the body of this youth was found in the street one morning, the Germans, in reprisal for the loss of their youthful agent, immediately seized the headquarters of the Medical Association and blew the building up, destroying all records and the Association's priceless collection of books.

The new *Domus Medica*, the former residence of a Danish nobleman, was purchased after the war and, with ample facilities, houses both the national association and the Copenhagen Medical Society, representing a considerable proportion of the parent body, since over a quarter of Denmark's population lives in the capital city.

In the furnishing of this new home a chandelier and tall clock were donated by the Norwegian Medical Association, nearly destitute itself as a result of Norway's occupation; a library and reading room were equipped by the medical profession of Sweden and are decorated in Sweden's blue and yellow.

As a practical matter of mutual benefit, the rooms of an upper floor are rented to Copenhagen students who are sons of Danish physicians.

CLOUD OF WITNESSES

THE Council of the Massachusetts Medical Society at a stated meeting held on February 7, 1951, authorized the Secretary of the Society "to maintain a list of physicians willing to assist in the defense of malpractice suits against members of the Society." This vote was taken on recommendation of the Advisory Committee on Malpractice Insurance.

In again calling this action of the Council to the attention of the fellows of the Society, the point should be made clear that its intention is to serve justice and justice only. Regardless of any implication that might be read into such a recommendation by those ignorant of the ethics of the Society, this is not an invitation to anyone to distort the shape of medical evidence so that it will favor a fellow physician. Its sole purpose is to discover truth and to give all the proper support that can be given to a member of the Society unjustly accused of malpractice.

The Secretary was not asked to assume the impractical task of going out to find physicians who will permit their names to be placed on such a list. Those who are willing to perform this important duty must volunteer for it.

Hygienic Use of Alcohol. — An address by F. M. Robertson, M.D., on the medical and hygienic use of this potent stimulus, sent from Charleston, S. C., cannot receive the attention its merits deserve for the present week. He writes well, and his teetotal reasoning is truly philosophical.

Boston M. & S. J., *December 24, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

SEGALL — Samuel K. Segall, M.D., of New Bedford, died on September 6. He was in his sixty-ninth year.

Dr. Segall was graduated from Tufts College Medical School in 1912. He was a member of the New Bedford Medical Society.

His widow and a daughter survive.

SHERMAN — Warren H. Sherman, M.D., of Lowell, died on November 9. He was in his seventy-fourth year.

Dr. Sherman received his degree from Bowdoin Medical School in 1905. He was a fellow of the American Medical Association.

His widow survives.

THOMSON — Robert S. Thomson, M.D., of Fitchburg, died on November 19. He was in his fortieth year.

Dr. Thomson received his degree from Harvard Medical School in 1938.

His widow survives.

BOSTON MEDICAL LIBRARY

NOTES

Exhibit on Medical Discoveries Announced in 1901

An exhibit of important medical papers that appeared in the year 1901 is now on display at the Library. This group includes the original announcements of the discovery of the trypanosome of sleeping sickness (Dutton and Forde), the demonstration of complement fixation (Bordet and Gengou), the isolation of adrenaline (Takamine) and tryptophane (Hopkins and Cole), the observation of isoagglutination (Landsteiner) and the ester method of isolating amino-acids (Emil Fischer).

Popular Hygiene

Professor Luigi Belloni of Milan has again rendered a great service to medical history, this time by reproducing the tract of Antonius Beniveni (1443–1502), *De regimine sanitatis ad Laurentium medicem*, not published in the fifteenth century but existing in manuscript (Cod. Marc. lat. vii, 29). The tract is a hygienic-prophylactic regimen to be used during the plague and was written for Lorenzo the Magnificent. A preface discusses the history of science and medicine during the transition between the medieval and Renaissance periods.

The pamphlet was published in July, 1951, in Turin, on the occasion of the second congress of the Società Italiana di Patologia. It is a beautiful piece of printing.

History of Physiology

Professor J. Joaquin Izquierdo has published an interesting monograph on the history of physiology in Mexico and of the University of Mexico (1580 to 1951).[1] Marcos José Salgado[2] wrote in 1727 the first book on physiology to be published in the Americas. An interesting plate shows a niche in the university library, housing the busts of three luminaries in experimental physiology, William Harvey, Claude Bernard and Ivan Petrovich Pavlov.

Rheumatism

La Ligue Internationale Contre le Rheumatisme has issued its yearbook for 1950. The text is presented in English, French and Spanish. It contains the history, by-laws, organization and lists of members. The publication should be of value to all persons interested in rheumatic diseases, as it presents the story of international co-operation in this important field of medicine and lists about 2500 persons in 32 societies in 18 European and 10 American countries, Australia and New Zealand.

Copies, at $1.00 each, may be obtained from Dr. Robert M. Stecher, 3395 Scranton Road, Cleveland 9, Ohio.

Congress on Digestion and Nutrition

The VI Congreso Español de Patología Digestiva y de la Nutrición was held in Santander, September 5–8, 1951. Forty-three papers were read on the medical and surgical aspects of the specialties considered. At the opening session papers were read on syndromes following gastrectomy and on cancer of the colon. Dr. Hillemand, president of the French society of gastroenterologists, and Dr. McNee, president of the English society, read papers by invitation, on polyposis of the colon and on epidemic infectious hepatitis, respectively.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts follows:

Orthopedic Clinic	Date	Clinic Consultant
Haverhill	January 2	William T. Green
Greenfield	January 3	Charles L. Sturdevant
Lowell	January 4	Albert H. Brewster
Salem	January 7	Paul W. Hugenberger
Gardner	January 8	Carter R. Rowe
Brockton	January 10	George W. Van Gorder
Lynn*	January 14	Daniel M. Killoran John J. Crowley
Springfield	January 15	Garry deN. Hough, Jr.
Pittsfield	January 16	Edward J. Coughlin, Jr.
Hyannis	January 17	Paul L. Norton
Worcester	January 18	John W. O'Meara
Fall River	January 21	David S. Grice

Rheumatic-Fever Clinics	Dates
North Reading	January 8, 15, 22, 29
Fitchburg	January 2, 9, 16, 23, 30

Plastic Clinics	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon
Western Massachusetts	Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

CREDIT WHERE DUE

To the Editor: For the sake of accuracy I would like to call your attention to the editorial "Preprofessional Education for Medicine," which appeared in the November 8 issue of the *Journal*.

The survey of medical schools is not being conducted by the American Medical Association but is sponsored jointly by the Association of American Medical Colleges and the American Medical Association, and the preprofessional section of the study is being carried out through a grant of $65,000 from the Markle Foundation to the Association of American Medical Colleges. The editorial discussed the preprofessional part of the study, a concise description of which will be found on page 28 of the 1950 Annual Report of the Markle Foundation (14 Wall Street, New York 5).

The Association of American Medical Colleges is doing some extremely important work. This is unknown not only to the public in general but, it would seem, to the medical profession as well.

William Swanberg, Managing Editor
Journal of Medical Education
Chicago, Illinois

Note: The Association of American Medical Colleges is not mentioned in the report from which the source material of the editorial in question was drawn. (Carman, H. S. Preprofessional survey of medical education: progress report. *J. A. M. A.* **146**:81-85, 1951.)

The association is, however, credited in the Markle Foundation Report for 1950 as the organization to which the grants, totaling $65,000, were made. The Association of American Medical Colleges is also mentioned elsewhere in the same report as "the only organization in the United States devoted exclusively to furthering and improving medical education, directed by medical educators and supported by the medical schools themselves."

Ed.

CEREBRAL-PALSY DIAGNOSTIC SERVICE

St. Christopher's Hospital for Children, in co-operation with the United Cerebral Palsy Fund and the Department of Pediatrics of Temple University School of Medicine, announces the establishment of a diagnostic service for neuropathologic studies of cerebral palsy.

The facilities of any single institution for investigation of neuropathologic problems are limited by the relatively small number of autopsies performed on children with neurologic disorders and by the inaccessibility of facilities for detailed histologic examination of the central nervous system. This new service, under the direction of Dr. James B. Arey and Dr. Waldo E. Nelson, with Dr. Ernest Spiegel as consulting neuropathologist, has been formed in an effort to make these facilities available to more physicians and hospitals.

The purpose of this service will be to correlate the clinical course and pathologic findings in children in whom a disease of the central nervous system is suspected or in whose case the diagnosis of cerebral palsy has been entertained or established.

The institution submitting the clinical history and the brain of such a patient will receive a detailed report, together with a pertinent bibliography and representative histologic sections, within six months after the specimen is received. Transportation costs and suitable containers will be furnished on application to Dr. James B. Arey, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pennsylvania.

James B. Arey, M.D., Pathologist
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

BOOK REVIEW

Electroencephalography in Clinical Practice. By Robert S. Schwab, M.D. 4°, cloth, 195 pp., with 106 illustrations. Philadelphia: W. B. Saunders Company, 1951. $6.50.

The electroencephalograph, as an essential diagnostic piece of apparatus, has become universal in all large and many small progressive medical centers. The machine, however, is costly; the technical skill required to maintain it is considerable; and interpretation of the records is open only to those specially trained. Qualified electroencephalographers are now certified by membership in national and international organizations, a development that has taken place in the last fifteen years. Although electric activity of the brain was recognized as early as 1875 by Caton, the possibility of measuring electrical currents produced by the living brain and the use of these recordings as a diagnostic approach to some of the problems connected with psychiatry was the work of Hans Berger in Germany, in 1924 and in subsequent years. Berger's discovery was accepted ten years later, by Adrian and Matthews, of England. Subsequently Hallowell Davis, Herbert Jasper, Grey Walter, Robert S. Schwab and others added to our knowledge, and the electroencephalograph became a practical instrument of clinical importance.

The new specialty has now acquired, as Schwab points out, the maturity and dignity of other diagnostic procedures. Both the technic and the interpretation, however, are far from satisfactory. Fortunately, the skilled workers in this field are keeping in close touch with the basic sciences, which have already added so much to the setting of technical standards. The electroencephalogram today is the product of team play by clinicians, physiologists, physicists and engineers. Means are being developed throughout the world for examination and certification of commercial apparatus, the training of both technicians and physicians and the screening and supervision of published material. The medical world can take pride in this orderly development and will note with approval that this monograph exemplifies all that is best in this modern discipline.

The book under consideration is a practical treatise, covering briefly but adequately the electroencephalogram and the apparatus used to record it. Particular attention is directed to the electroencephalogram in epilepsy, brain tumors and the psychoses. A final chapter deals with the organization of a laboratory, the training of a staff and the interpretation of records. The author's wide experience

and sound practice make him fully qualified to write an authoritative book, and this he has done in an admirable manner. It should become a standard text for all clinicians and should be found in all hospitals and libraries. Let the reader note, however, that electroencephalography is not a specialty to be acquired quickly; no small apparatus of less than four channels is considered adequate. Most laboratories use six channels, and many prefer eight. The cost of a machine is $2500 to $3500, its life five to nine years. The instrument is one of extreme delicacy and precision. Hospitals or clinics contemplating the erection of an electroencephalographic laboratory should apply to the American Electroencephalographic Society in this country for data on minimum requirements.

The book carries a glossary, an index and many charts and photographs, as well as references to the literature. Easy to understand and clearly written in orderly fashion, it is strongly recommended as a definitive text.

HENRY R. VIETS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Diabetes Insipidus. By Harry Blotner, M.D., associate visiting physician, Beth Israel Hospital, Boston, Massachusetts. Edited by Henry A. Christian, M.D., LL.D. 8°, cloth, 194 pp., with 24 illustrations. New York: Oxford University Press, 1951. $4.50. (Reprinted from *Oxford Loose-Leaf Medicine* with the same pagination.)

This monograph presents a comprehensive study of diabetes insipidus. The literature of the subject from the earliest times to date is mentioned and evaluated throughout the text. There is a good index and the monograph is well published.

Nutrition and Alcoholism. By Roger J. Williams, Ph.D. 12°, cloth, 82 pp. Norman, Oklahoma: University of Oklahoma Press, 1951. $2.00.

In this small volume the author advocates a treatment that utilizes highly potent food elements for the cure of alcoholism. The treatment is said to be harmless because no foreign agent is introduced into the body.

Blood Groups in Man. By R. R. Race, Ph.D. (Cantab.), M.R.C.S. (England), director, Medical Research Council Blood Group Research Unit, Lister Institute, London, and Ruth Sanger, Ph.D. (London), Medical Research Council Blood Group Research Unit, Lister Institute, London. With a foreword by Prof. R. A. Fisher, F.R.S. 8°, cloth, 290 pp., with 26 illustrations and 87 tables. Springfield, Illinois: Charles C Thomas, 1950. $6.50.

This new monograph is concerned with the various blood groups in relation to their inheritance. The final chapter is devoted to problems of parentage and identity. Lists of references are appended to the various chapters, and there are indexes of authors and subjects. The volume should be in all collections on blood and transfusion.

Paracelsus, Selected Writings. Edited with an introduction by Jolande Jacobi and translated by Norbert Guterman. 8°, cloth, 346 pp., with 148 illustrations. New York: Bollingen Foundations Incorporated, 1951. $4.50. (Bollingen Series XXVIII.)

This anthology of selections from the works of Paracelsus was first published in German in 1942. A short biography precedes the text proper and there is an index to sources and a bibliography. The lack of an index detracts from the reference value of the book. The publishing is good and the book should be in all medical-history collections.

Nutrition and Chemical Growth in Childhood. Volume III, Calculated data. By Icie G. Macy, Ph.D., Sc. D., director of the Research Laboratory, Children's Fund of Michigan, chairman, Maternal and Child Feeding Committee, Food and Nutrition Board, National Research Council, and consultant for nutrition to the pediatric staff of the Children's Hospital of Michigan. With a foreword by Helen A. Hunscher, Ph.D., head of the Department of Home Economics, Western Reserve University. 8°, cloth, 711 pp., with 732 tables. Springfield, Illinois: Charles C Thomas, 1951. $8.00.

This statistical volume completes the set of three volumes of a standard reference work in the field of pediatrics. An index for the complete work is appended to the text of this volume. The price is surprisingly low for this type of book. The set should be in all collections on pediatrics.

The Kidney: Structure and function in health and disease. By Homer W. Smith, Sc.D., M.S., professor of physiology, New York University College of Medicine. 8°, cloth, 1049 pp., with 153 illustrations and tables. New York: Oxford University Press, 1951. $12.50. (Oxford Medical Publications.)

This comprehensive monograph is devoted principally to the physiology of the kidney and its various aspects. Part 4 discusses disturbances of renal function and diseases of the kidney and urinary tract. The pertinent literature is evaluated throughout the text. There is a bibliography of 3300 references. The book is well published and should be in all medical libraries.

Allergy: Facts and fancies. By Samuel M. Feinberg, M.D., associate professor of medicine, chief of Section of Allergy and director of Allergy Research Laboratory, Northwestern University Medical School, and attending physician, Passavant Memorial Hospital. 12°, cloth, 173 pp. New York: Harper and Brothers, 1951. $2.50.

This small book, written for the laity by a well known specialist, covers every aspect of allergy. There is a good index and the book is especially suitable for public libraries.

Clinical Heart Disease. By Samuel A. Levine, M.D., clinical professor of medicine, Harvard Medical School, physician, Peter Bent Brigham Hospital, Boston, consultant cardiologist, Newton–Wellesley Hospital, and physician, New England Baptist Hospital. Fourth edition. 8°, cloth, 556 pp., with 192 illustrations. Philadelphia: W. B. Saunders Company, 1951. $7.75.

The last edition of this standard textbook on the heart was published in 1945. The present edition has been revised to bring the subject up to date. The chapter on electrocardiography has been completely rewritten. New material has been added on the use of antibiotics in the treatment of bacterial endocarditis, the use of anticoagulants in coronary thrombosis, and the catheterization of the heart. There is a good index and the book is well published. It should be in all medical libraries and in all collections on the heart.

The Neurosurgical Treatment of Traumatic Paraplegia. By J. Lawrence Pool, M.D., professor of neurological surgery, Columbia University College of Physicians and Surgeons. 8°, cloth, 107 pp., with 24 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $3.00. (Publication Number 83, American Lecture Series.)

This small monograph discusses the physiology of spinal-cord injury, its diagnosis and treatment in general, and laminectomy in particular. The final chapter concerns the management of the paraplegic patient. A good bibliography concludes the text and the monograph is well illustrated.

Annotated Bibliography of Vitamin E, 1940–1950. Compiled by Philip L. Harris and Wilma Kujawski of the Research Laboratories of Distillation Products Industries, Rochester, New York (Division of Eastman Kodak Company). 4°, paper, 184 pp. New York: The National Vitamin Foundation, Incorporated, 1950. $3.00.

This important bibliography of 1562 references is arranged in 8 categories, including one on medical and therapeutic use. An author index concludes the text.

Tuberculosis Among Children and Adults. By J. Arthur Myers, M.D., Ph.D., physician in charge, Chest Clinic, Students Health Service, University of Minnesota, chief of Tuberculosis Service, Minneapolis General Hospital, and professor of medicine, preventive medicine and public health, Medical and Graduate Schools, University of Minnesota. With an introduction by Allen K. Krause, M.D. Third edition. 8°, cloth, 894 pp., with 177 illustrations and 7 tables. Springfield, Illinois: Charles C Thomas, 1951. $12.50.

The first edition of this standard reference work was published in 1930 and was devoted exclusively to tuberculosis in children. In the second edition (1938) young adults were included. Because of the noticeable shift in the age period at which the height of tuberculosis mortality is reached, this third edition includes adults. The text is divided into four parts on infancy, childhood, young adults and recent progress in control. A list of references is appended to each chapter and there is a comprehensive index of subjects and authors. The book should be in all collections on tuberculosis and on pediatrics.

Fever Therapy. By H. Worley Kendell, M.D., professor of physical medicine and rehabilitation, University of Illinois Research and Educational Hospitals, Chicago, Illinois. 8°, cloth, 101 pp., with 15 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 80, American Lecture Series.)

This small monograph discusses physically induced fever as a therapeutic agent. Its use in syphilis, gonococcic infections, rheumatism and ocular diseases is mentioned. A bibliography of 136 references concludes the text.

Hypertension: A symposium held at the University of Minnesota on September 18, 19, and 20, 1950, in honor of Elexious T. Bell, M.D., Benjamin J. Clawson, M.D., and George E. Fahr, M.D. Edited by Elexious T. Bell. 8°, cloth, 573 pp., with illustrations and tables. Minneapolis: University of Minnesota Press, 1951. $7.50.

This honorary volume contains 30 papers by 24 well known specialists on the various aspects of hypertension. A bibliography of 35 pages arranged by chapters concludes the text. The book is well illustrated and the publishing is excellent. The lack of an index detracts from its reference value. It should be in all medical libraries and available to all persons interested in the subject.

Herzschalldiagnostik in Klinik und Praxis. Eine Einführung in den praktischen Gebrauch der Herzschallschreibung. By Jorgen Schmidt-Voigt, Dr. Med., Facharzt für innere Medizin, Chefarzt am Städt. Krankenhaus Eppstein im Taunus. 8°, paper, 116 pp., with 33 illustrations and 1 table. Stuttgart: Georg Thieme, 1951. DM 9.60.

This small volume discusses the various cardiac sounds, both normal and disordered. There is a good subject index and the small book is well published. It should prove valuable to German-reading physicians.

Your Sinus Troubles and Treatments: An authoritative explanation for the layman, with recommendations for the treatment of your sinus conditions, colds, hay fever and other allergies. By Friedrich S. Brodnitz, M.D. 12°, cloth, 241 pp., with 9 illustrations. New York: Abelard Press, 1950. $2.50.

In this book, written for laymen, the common cold and sinus complications are discussed. The chapter on sneezing without having a cold is particularly interesting. It discusses the use of the so-called "cold tablets" and their misuse in allergic conditions.

A Few Buttons Missing: The case book of a psychiatrist. By James T. Fisher, M.D., and Lowell S. Hawley. 8°, cloth, 282 pp. Philadelphia: J. B. Lippincott Company, 1951. $3.50.

In this book Dr. Fisher tells in an informal way the story of his life as a psychiatrist. Included are case histories of all types of psychiatric patients, from neurotics to manic depressives and schizophrenics, enlivened by appropriate anecdotes. Dr. Fisher, born in Boston, graduated from Harvard Medical School in 1896. He has studied at various times in foreign cities and has made nineteen trips abroad. His collaborator, Mr. Hawley, has been a teacher and newspaper and radio writer. The book should be in all medical history collections.

Philosophy for the Common Man. By Heinrich R. Wolf. 8°, cloth, 189 pp. New York: Philosophical Library, 1951. $3.50.

The author, a practicing physician, discusses in this small book basic philosophic programs in a simple terminology.

Principles and Practice of the Rorschach Personality Test. By W. Mons, M.R.C.S., L.R.C.P. Second edition. 8°, cloth, 176 pp. Philadelphia: J. B. Lippincott Company, 1951. $4.00.

The first edition of this manual was based on a large personal experience. In this second edition the author has brought his text up to date by some additions and minor alterations. He has replaced the examples used in the first edition with new ones to better illustrate the essential character of the test.

Conference on Problems of Aging: Transactions of the twelfth conference, February 6-7, 1950, New York. Edited by Nathan W. Shock, chief, Section on Gerontology, National Heart Institute, National Institutes of Health, and the Baltimore City Hospitals, Baltimore, Maryland. 8°, cloth, 215 pp. New York: Josiah Macy, Jr., Foundation, 1951. $3.50.

The participants in this conference discussed the intrapersonal and interpersonal aspects of gerontology, its relation to clinical medicine and its economic and psychopathological aspects.

Emotional Factors in Cardiovascular Disease. By Edward Weiss, M.D., professor of clinical medicine, Temple University School of Medicine. 12°, cloth, 81 pp. Springfield, Illinois: Charles C Thomas, 1951. $2.50. (Publication Number 97, American Lecture Series.)

This small monograph discusses anxiety and the heart, "functional" heart disease and its treatment, neurocirculatory asthenia, hypertension and anxiety, low blood pressure and organic heart disease in relation to anxiety, and psychosis and cardiac disease.

Problems of Consciousness: Transactions of the first conference, March 20-21, 1950, New York. Edited by Harold A. Abramson, M.D., department of physiology, Columbia University College of Physicians and Surgeons. 8°, cloth, 200 pp. New York: Josiah Macy, Jr., Foundation, 1951. $3.00.

Five authorities in their particular fields presented five papers at this new conference. They comprised the sleep-wakefulness cycle, the psychoanalytic concept of sleep and dream, the perception of pain and some factors that modify it, the phenomena of hypnosis, and consciousness and the chemistry of time.

An Introduction to Modern Psychology. By O. L. Zangwill. 16°, cloth, 227 pp., with 20 illustrations. New York: Philosophical Library, 1950. $3.75. (Home Study Books.)

This small book gives an account of the origin of modern psychology and its development as a biologic science. The chapters comprise the background of modern psychology; a survey of experimental psychology: sensory processes, learning and intellect; modern physiologic psychology: brain and mind; appetite, instinct, and emotion; intelligence and mental measurement; psychoanalysis; problems of personality; and psychology and the future. The text is well written; there is a good index and the publishing is well done. The book is suitable for the reference section of medical libraries.

After the A Bomb: Emergency care in atomic warfare. Edited by Charles F. Behrens, M.D., commanding officer, Naval Medical Research Institute, National Naval Medical Center, and director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department. 12°, cloth, 182 pp. New York: Thomas Nelson and Sons, 1951. $2.50.

This manual is the joint work of nine authorities on radiation. The various papers provide a practical consideration

of the medical responsibilities at the working levels applicable to disaster conditions. They discuss the picture of disaster, special weapons, rescue and first aid, care of burns and other trauma and treatment of radiation in mass casualties, remedial agents, hospital and public-health problems, and the management of personnel contamination with radioactive material. There is a good index and the small volume is well published. It should be in all medical libraries.

Nerve Impulse: Transactions of the first conference, March 2-3, 1950, New York. Edited by David Nachmansohn, Department of Neurology, Columbia University College of Physicians and Surgeons. 8°, cloth, 159 pp. New York: Josiah Macy, Jr., Foundation, 1951. $3.00.

This new conference was participated in by fourteen members. Five papers were read on the potentialities and limitations of electrophysiology, limitations and potentialities of the biochemical approach to problems of nerve conduction, comparative physiology, histologic studies, and ion exchange and permeability. The various series of conferences published by the Foundation are valuable and should be in the reference collections of all medical libraries.

Factors Regulating Blood Pressure: Transactions of the fourth conference, February 23-24, 1950, New York. Edited by Benjamin W. Zweifach and Ephraim Shorr, M.D., Department of Medicine, Cornell University Medical College. 8°, cloth, 219 pp. New York: Josiah Macy, Jr., Foundation, 1951. $3.00.

Ten papers on various aspects of hypertension were presented at this conference. Included were anatomic considerations, histologic changes in the liver and kidney of rats made hypertensive by a choline-deficient diet, clinical criteria for diagnosis and classification, renal circulatory adjustments, relation of endocrine organs to essential hypertension, a comparative study of experimental renal and human essential hypertension with respect to VEM and VDM, and three papers on various aspects of renin. List of references are appended to the various papers.

Problems of Infancy and Childhood: Transactions of the fourth conference, March 6-7, 1950, New York. Edited by Milton J. E. Senn, M.D., Departments of Pediatrics and Psychiatry, Yale University School of Medicine. 8°, cloth, 181 pp. New York: Josiah Macy, Jr., Foundation, 1951. $2.25.

This conference was suggested by the Fact Finding Committee of the Mid-Century White House Conference. Three topics were discussed: cultural determination of parental attitudes; the relations in the social structure, particularly family structure and parental behavior; a consideration of some problems in the ontogeny of family life and social adjustments in various infrahuman attitudes; and working toward healthy personality.

Annual Review of Medicine: Volume 2, 1951. Windsor C. Cutting, M.D., editor, and Henry W. Newman, M.D., associate editor, both of Stanford University School of Medicine. 8°, cloth, 485 pp. Stanford, California: Annual Reviews, Incorporated, 1951. $6.00.

This volume follows the pattern of the first volume for 1950. All eighteen articles are documented with long lists of references. The text concludes with an annotated list of reviews in medicine published between November, 1949, and January, 1951, comprising twelve pages. There are indexes of authors and subjects and the publishing is excellent. The review provides an excellent summary of the progress in medicine for the year previous to publication.

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, and physician-in-chief, Peter Bent Brigham Hospital, Boston. With the collaboration of Peter H. Forsham, M.D., M.A. (Cantab.), instructor in medicine, Harvard Medical School, and junior associate in medicine, Peter Bent Brigham Hospital, and Kendall Emerson, Jr., M.D., assistant professor, Harvard Medical School, and senior associate in medicine, Peter Bent Brigham Hospital. Second edition. 8°, cloth, 182 pp., with 35 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $5.50. (Publication Number 29, American Lecture Series.)

The first edition of this monograph was published in 1949 and was so well received that a new edition is now required after two years. A brief introduction outlines the history of the condition from the time of Addison (1855) to the present. The material on Addison's disease and adrenal cortical insufficiency is comprehensive in scope, covering all aspects of the conditions. A bibliography of 131 titles is appended to the text. The lack of an index is unfortunate in such an important monograph.

Clinical Electrocardiography. By Ashton Graybiel, Captain (MC), United States Navy, and director of research, United States Naval School of Aviation Medicine. 8°, cloth, 198 pp., with 140 illustrations. New York: Thomas Nelson and Sons, 1951. $5.00.

This monograph is intended as a practical guide for the use of the method in medical practice. It is an amplified version of the chapter in *Nelson's Loose-Leaf Medicine.* There is an index and the publishing is excellent.

Proceedings of the Second Clinical ACTH Conference. Volume 1: Research. Volume 2: Therapeutics. Edited by John R. Mote, M.D. 8°, cloth. Volume 1, 531 pp., with 276 illustrations and 52 tables. Volume 2, 716 pp., with 311 illustrations and 81 tables. Philadelphia: The Blakiston Company, 1951. $8.50 per volume.

The second conference was sponsored by the Armour Company and held in Chicago on December 8 and 9, 1950. Forty-nine papers are contained in the research volume, fifty-three in the clinical volume. The papers are too numerous and too varied in aspect to permit enumeration. The publishing is excellent. An index would make the volumes more valuable for reference purposes. The set should be in all medical libraries.

Treatment of the Nephrotic Syndrome. By Lee E. Farr, M.D., chairman, Medical Department, Brookhaven National Laboratory, and physician-in-chief, Brookhaven National Laboratory Hospital. 8°, cloth, 61 pp. Springfield, Illinois: Charles C Thomas, 1951. $1.75. (Publication Number 64, American Lecture Series.)

In this monograph the author discusses the treatment of edema, malnutrition, the renal lesion and complication, the nephrotic crises, cortisone, ACTH and nitrogen mustard. A bibliography of 71 titles concludes the text.

Handbook of Nutrition: A symposium. Prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association. Second edition. 8°, cloth. 717 pp., with 35 illustrations, 28 tables and 7 charts. New York: The Blakiston Company, 1951. $4.50.

This standard handbook was first published in 1943; it is brought up to date in this new edition. The various papers have been reprinted from the *Journal of the American Medical Association,* with additions. The symposium is by thirty-three leading authorities and was prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association. The material is divided into four principal categories: individual nutrients, nutritional needs, nutritional deficiencies and foods and their nutritional qualities. The various papers are documented with references and there is a good index. The book should be in all reference collections on foods and nutrition.

Roentgenologic Diagnosis of Diseases of Bones. By David G. Pugh, M.D., assistant professor of radiology, Mayo Foundation, Graduate School, University of Minnesota, and consultant, Section on Roentgenology, the Mayo Clinic. 8°, cloth, 316 pp., with 307 illustrations. New York: Thomas Nelson and Sons, 1951. $6.00.

This volume is essentially an atlas; it presents illustrations and discussions of diseases of the bone, from endocrine disturbances to tumors and congenital dislocation of the hip. A bibliography of nine pages concludes the text, and there is a good index. The publishing is well done. The book should be in all collections on the subject.

Cystektomie beim Blasenkrebs. By Prof. Dr. H. Boeminghaus. 8°, paper, 84 pp., with 56 illustrations. Stuttgart: Georg Thieme, 1951. Kartoniert DM 11.50. Distributed by Grune and Stratton, Incorporated, New York.

This is a small but comprehensive monograph on cystectomy for cancer of the bladder. Total, abdominal, abdominovaginal and sacral cystectomy and pelvectomy are described and illustrated with excellent drawings. The concluding chapters discuss after-treatment and late results, including mortality statistics. The publishing is excellent.

Thyreotoxikosen und antithyreoidale Substanzen. By Hans W. Banso, apl. Professor an der Universität Hamburg, Chefarzt der I. Med. Abtlg. des Allg. Krankenhauses St. Georg, Hamburg. 8°, paper, 100 pp., with 4 illustrations. Stuttgart: Georg Thieme, 1951. Kartoniert DM 11.40.

This monograph on thyrotoxicosis and antithyroidal substances is comprehensive in its scope and is based on the pertinent literature. There is a bibliography of three and a half pages and there are author and subject indexes. The publishing is well done and the monograph should be in all collections on the thyroid gland.

A Review of Medicine: By members of the faculty, Northwestern University Medical School. Benjamin Boshes, M.D., M.S., Ph.D., editor, associate professor of nervous and mental diseases, Northwestern University Medical School, attending neuropsychiatrist, Passavant Memorial and St. Luke's Hospitals, Chicago, and senior consultant in neurology, Veterans Administration Hospital, Hines, Illinois. Sixth edition. 4°, cloth, 814 pp. Chicago: The Chief Printing Company, 1951. $15.00.

This review, first published in 1940, was based on the mimeographed *Cook County Notes*. The book is an elastic compilation of the data taught in the classrooms of the Northwestern University Medical School. This sixth edition is essentially a new book, inasmuch as eight years have elapsed since the fifth edition appeared in 1942. The text has been thoroughly revised and reorganized and the type completely reset. The work is the joint effort of 33 members of the faculty and covers the fields of medicine, surgery and the specialties. The volume is not intended as a textbook or as a substitute for a review of current literature. A comprehensive index concludes the text and the publishing is excellent.

NOTICES

NEW ENGLAND CONFERENCE ON ALLERGY AND RELATED SUBJECTS

The fourth meeting of the New England Conference on Allergy and Related Subjects will be held on Wednesday, January 23, 1952. The subject will be "Pulmonary Function in Asthma and Emphysema." A clinical session will be given from 3:00 to 5:00 p.m. at Boston University School of Medicine, 80 East Concord Street. Reservations for dinner (7:00 p.m., at the Copley Plaza Hotel) may be obtained by writing to Dr. I. W. Schiller, 65 East Newton Street. An evening program, also at the Copley Plaza Hotel, will be presented from 8:30 to 10:30 p.m.

BOSTON GASTROENTEROLOGICAL SOCIETY

The Boston Gastroenterological Society will present a symposium on early diagnosis of carcinoma of the stomach on January 17, 1952, at 8:30 p.m., in the amphitheater of St. Elizabeth's Hospital.

PROGRAM

X-Ray Characteristics of Gastric Carcinoma — Dr. William A. Carey.

Cytologic Studies in Gastric Carcinoma — Dr. Stanley L. Robbins.

Abnormal Electric Potentials in Gastric Disorders — Dr. Henry M. Lemon.

All interested physicians and medical students are invited to attend.

TUFTS MEDICAL ALUMNI LECTURE

The annual Tufts Medical Alumni Lecture will be given on Thursday, January 10, 1952, at 11:00 a.m., at Tufts Medical School by Dr. Jesse E. Edwards (M'35), consulting physician, Section of Pathologic Anatomy, Mayo Clinic, and associate professor of pathologic anatomy, Mayo Foundation, University of Minnesota. Dr. Edwards will speak on "Advances in Pathology of Cardiovascular Diseases."

Physicians and medical students are invited to attend.

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The 111th winter meeting of the Essex North District Medical Society will take place, as previously announced, on January 9, 1952. Dinner will be served at 1:15 p.m. Dr. Francis D. Moore, surgeon-in-chief, Peter Bent Brigham Hospital, will discuss "The Management of Burns." The meeting will be held at the Haverhill Country Club, rather than at the Pentucket Club, as formerly planned.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The next regular meeting of the New England Society of Anesthesiologists will be held on Tuesday evening, January 8, 1952, at the Millville Inn, Concord, New Hampshire.

PROGRAM

Cocktails	5:00–5:45 p.m.
Dinner	5:45–7:00 p.m.
Business meeting	7:00–7:30 p.m.
Scientific meeting	7:30–9:00 p.m.

SCIENTIFIC PROGRAM

Cardiac Irritability and the Mechanism of Fibrillation. Dr. John Abajian, Burlington, Vermont.

Pulmonary Function Studies in Anesthesiology. Dr. Carl Hellijas, Hartford, Connecticut.

The Post-Graduate Education Committee of the New England Society of Anesthesiologists will present a series of six sessions, to be held on January 5, February 2, March 1, April 5 and May 3. The sessions will include morning visits to Boston hospitals and round-table luncheon discussions and afternoon lectures at Massachusetts General Hospital. The registration fee will be $5.00; residents and medical students will be admitted without fee. Further information may be obtained by writing to Dr. M. Gene Black, 575 Beech Street, Holyoke.

POSTDOCTORAL FELLOWSHIP

The National Research Council, Washington, D. C., has announced the availability of Merck Postdoctoral Fellowships in the Natural Sciences for 1952-1953. All fields of chemistry and biology, including the preclinical medical sciences, are open to applicants.

The fellowships carry stipends ranging from $3000 to $5000 in addition to travel expenses, and are offered annually to citizens of the United States with training in chemistry or biology equivalent to that represented by a Ph.D. degree. Applications must be filed with the Council before January 15, 1952.

The fellowships will be awarded as soon as possible after March 1, 1952. Appointments are for one year, with tenure beginning July 1, 1952, unless otherwise arranged. Study may be carried out in this country or abroad. A stipulation is that each Fellow shall pursue his research at an institution other than that at which he received his doctoral degree, except in unusual cases.

Further information and application blanks may be obtained from the Fellowship Office, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

(Notices concluded on page xi)

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NOTICES (*Concluded from page 996*)

UNITED STATES PUBLIC HEALTH SERVICE LABORATORY TRAINING COURSES

The Communicable Disease Center of the United States Public Health Service will present a series of laboratory refresher training courses throughout the year 1952. Application forms and further information may be obtained from the Chief, Laboratory Training Services, Communicable Disease Center, United States Public Health Service, P. O. Box 185, Chamblee, Georgia.

INTERNATIONAL DIABETES FEDERATION

A congress on diabetes, organized by the International Diabetes Federation, will be held at Leyden, The Netherlands, July 7-12, 1952. Further information may be obtained by writing to Dr. F. Gerritzen, 33, Prinsegracht, The Hague, Netherlands.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 21 AND 28 AND JANUARY 4. New England Deaconess Hospital Clinic. Page 548, issue of October 4.

DECEMBER 22. The Springfield Hospital. Page 832, issue of November 22.

DECEMBER 28. Symposium on Premedical Education. Page 916, issue of December 6.

JANUARY 5, FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post Graduate Education Course. Page 996.

JANUARY 7, FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

JANUARY 8. New England Society of Anesthesiologists. Page 996.

JANUARY 9. Essex North District Medical Society. Page 996.

JANUARY 10. Tufts Medical Alumni Lecture. Page 996.

JANUARY 10. The Recognition and Management of Common Kidney Diseases. Dr. Robert P. McCombs. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

JANUARY 14–19. School of Cytology. Page 956, issue of December 13.

JANUARY 17. Boston Gastroenterological Society. Page 996.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. New England Conference on Allergy and Related Subjects. Page 996.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–12. International Diabetes Federation. Notice above.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 9. Haverhill Country Club. (Note change of meeting place.)

HAMPSHIRE

JANUARY 2. Veterans Hospital, Northampton.

MARCH 5. Cooley-Dickinson Hospital, Northampton.

MAY 7. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 22. Veterans Administration Hospital, West Roxbury.

FEBRUARY 26. Boston Medical Library.

MARCH 25. Boston Medical Library.

APRIL 22. Boston Medical Library.

MAY 7. Place to be announced.

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 27

THURSDAY, DECEMBER 27

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. House of the Good Samaritan.

*3:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Medical Division Lectures. Mount Auburn Hospital, Cambridge.

FRIDAY, DECEMBER 28

*8:15 a.m. Insulin Allergy and Lipodystrophy. Drs. Page and Marble. Baker Clinic, New England Deaconess Hospital.

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.

*11:00 a.m.–12:00 m. Pediatrics. Worcester II. Mount Auburn Hospital, Cambridge.

*1:00–2:00 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

MONDAY, DECEMBER 31

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.

3:00–4:00 p.m. Gynecology Rounds. Mount Auburn Hospital, Cambridge.

5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

WEDNESDAY, JANUARY 2

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Meeting. Mount Auburn Hospital, Cambridge.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheatre, New England Deaconess Hospital.

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